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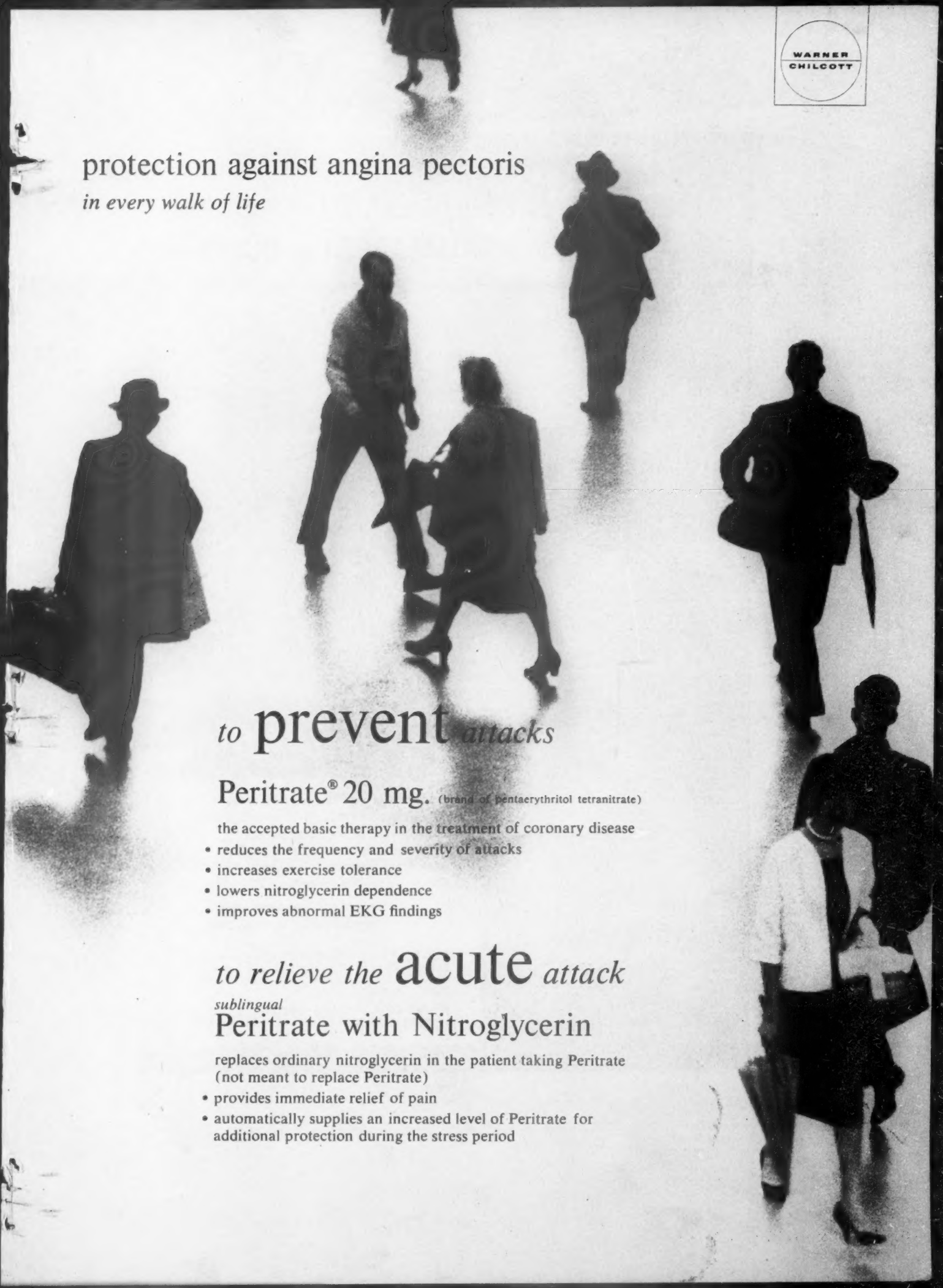
MANUSCRIPTS: All manuscripts should be typewritten double space and addressed to the Editorial Office of the Journal, 11 East 36th St., New York 16, N. Y. The top should be indicated on the back of each photograph. *Style for bibliography:* DOE, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

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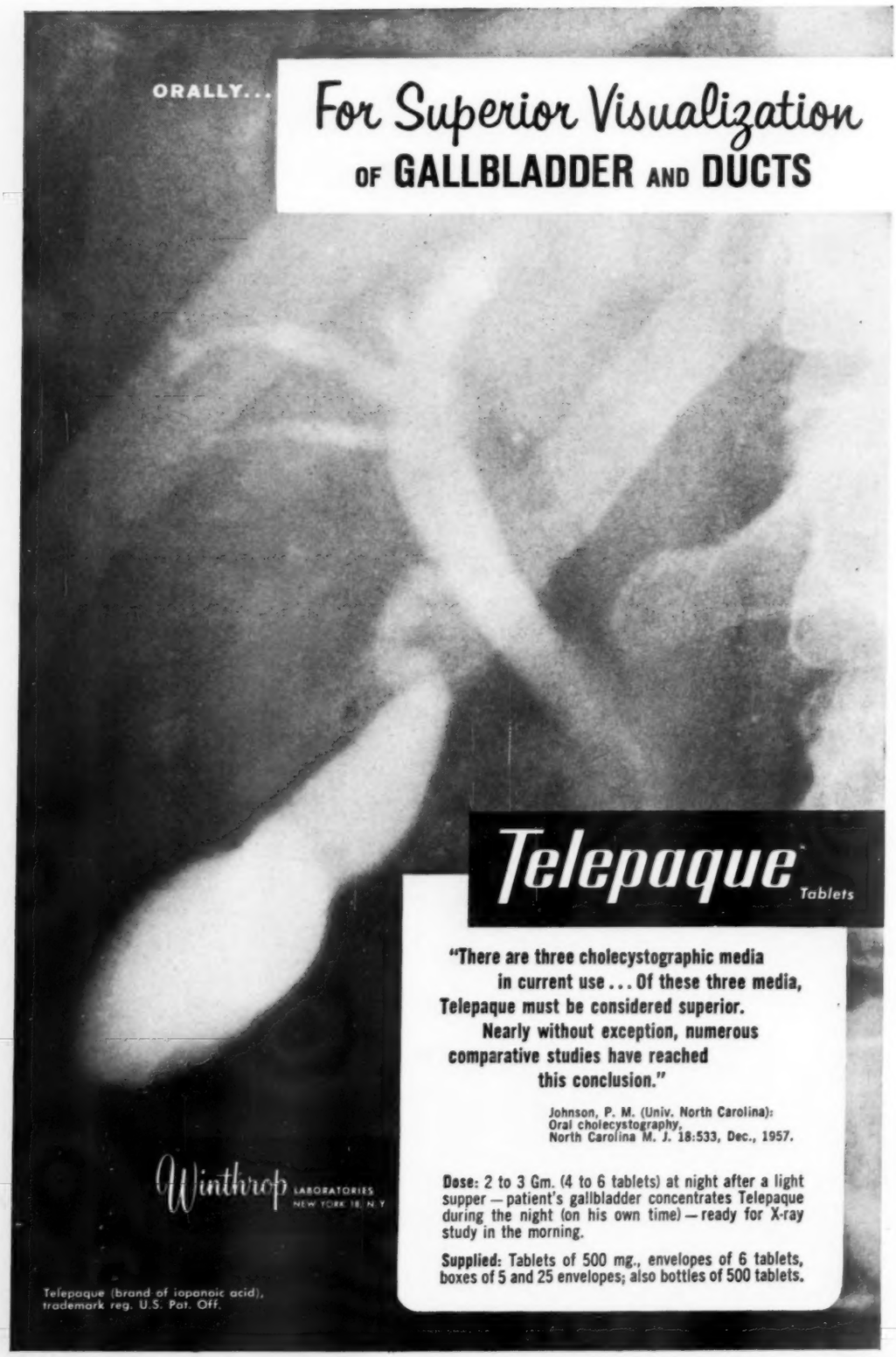
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The American Journal of Medicine

Vol. XXV DECEMBER, 1958 No. 6

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A Prospect of Richard Bright on the Centenary of His Death, December 16, 1858
ROBERT M. KARK 819

Clinical Studies

A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families. I. Streptococcal Disease Among Healthy Siblings
JOSEPH M. MILLER, SAMUEL L. STANCER AND BENEDICT F. MASSELL 825

A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families. II. Penicillin Prophylaxis Among Rheumatic Fever Subjects, Comparing Different Regimens JOSEPH M. MILLER, SAMUEL L. STANCER AND BENEDICT F. MASSELL 845

The value of penicillin prophylaxis in the prevention of recurrence of rheumatic fever is now well established but many details remain to be clarified. The first of the present carefully planned studies was directed toward the question of the advisability of extending prophylactic measures to the siblings of rheumatic children, who may be presumed, even though healthy, to have some enhanced predisposition to rheumatic fever. These children were found to have their full share and more of beta hemolytic streptococcal infection, and penicillin prophylaxis effectively prevented the development of rheumatic fever. The study brought out many interesting aspects of the natural history of streptococcal infection. The second paper is concerned chiefly with a comparison of the efficacy of orally administered penicillin G, 400,000 units per day, with that of intramuscularly administered benzathine penicillin G, 1.2 million units given at monthly intervals. Both were effective; each dosage form has advantages and disadvantages, to be taken into account for best results in individual circumstances.

Mucocutaneous-Ocular Syndrome with Intestinal Involvement. A Clinical and Pathological Study of Four Fatal Cases
JOHS BØE, JØRGEN B. DALGAARD AND DAG SCOTT 857

The mucocutaneous-ocular syndrome (or Stevens-Johnson syndrome as it is better known in this country) is an uncommon disease of obscure, possibly viral, origin which is probably more familiar to the ophthalmologist (as Behçet's syndrome) and dermatologist than to the internist. The present study describes four cases which came to autopsy, and stresses the involvement of the gastrointestinal tract. There was nothing specific about the intestinal lesions but the association with other manifestations of the mucocutaneous-ocular syndrome, not necessarily simultaneously, suggests

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A Summary Report on

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that implication of the gastrointestinal tract may be part of the disorder. Interestingly enough, the clinical and endoscopic characteristics of the lesions in the large bowel and rectum were indistinguishable from those in non-specific ulcerative colitis.

An Appraisal of Fulminant Meningococcemia with Reference to the Shwartzman Phenomenon . . . . . WILLIAM MARGARETTEN AND A. JAMES MCADAMS 868

Administration of adrenal steroids has become an accepted part of treatment in fulminant meningococcemia, in view of the high incidence of the Waterhouse-Friderichsen syndrome, although admittedly of dubious effectiveness. The present study questions the propriety of this therapy. In three cases bilateral renal cortical necrosis was found at necropsy, a lesion characteristic of the generalized Shwartzman phenomenon in rabbits, the development of which is facilitated by the administration of corticosteroids.

Pseudomonas Septicemia. Observations on Twenty-three Cases
CLAUDE E. FORKNER, JR., EMIL FREI, III, JOHN H. EDGCOMB AND JOHN P. UTZ 877

The authors make the inescapable point that the incidence of pseudomonas septicemia as a terminal event in chronic, debilitating diseases, such as leukemia, is increasing. The common clinical manifestations of this infection—such as the characteristic cutaneous lesions accompanying jaundice, neurological abnormalities, septic arthritis—should therefore be familiar, since specific antibiotic therapy must be initiated as soon as possible, preferably while awaiting confirmatory blood cultures. This need for haste is emphasized by the high mortality and the fact that so many superinfections with pseudomonas occurred, in the cases described, while the patients were receiving conventional broad-spectrum antibiotics.

Coccidioidal Pulmonary Cavitation . . . . . LEROY HYDE 890

Seventy-seven cases of pulmonary cavitation in coccidioidomycosis are presented. This complication occurs in about 0.1 per cent of all cases and is not always accompanied by positive skin tests or serological reactions. Conservative medical management led to spontaneous cavity closure in half the cases, with no new cavities. Surgical management resulted in 29 per cent of bronchopleural fistulas; new cavities appeared in 20 per cent of the cases. Even allowing for differences in the severity of the cases, this report reiterates the plea for conservative therapy of coccidioidal pulmonary cavitation.

Jaundice Associated with the Administration of Iproniazid. Report of Nine Cases
MELVIN KAHN AND VICTOR PEREZ 898

Nine cases of hepatotoxicity and marked jaundice associated with the use of iproniazid are described, two with fatal outcome. Examination of the liver in four cases uniformly revealed liver cell necrosis as the predominant finding, in some instances associated with more or less cholestasis. The clinical, chemical and pathological manifestations of iproniazid hepatotoxicity are delineated on the basis of this experience. It is concluded that, because of the hazard of hepatotoxicity, the use of iproniazid should be limited to cases in which the potential benefits of drug administration clearly outweigh the risks involved.

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is there any correlation between the amount of protein in urine and the grade of heart failure?

Yes. There is a fairly positive correlation.

Source—Race, G. A.; Scheifley, C. H., and Edwards, J. E.: Circulation *13*:329, 1956.

Proteinuria In Cardiac Failure

Grade	Mg. % Protein 0 10 20 30 40 50 60 70 80 90 100
I (31 patients)	8 patients; 23 patients
IV (11 patients)	7 patients; 3 patients; 1 patient

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Incorporation of Glycine-1-C^{14}, Glycine-2-C^{14} and Glycine-N^{15} into Uric Acid in Normal and Gouty Subjects
ALEXANDER B. GUTMAN, T'SAI FAN YÜ, HERMAN BLACK, ROSALYN S. YALOW AND SOLOMON A. BERSON 917

The incorporation of isotope-labeled glycine into uric acid was further investigated in an attempt to gain more insight into the nature of the metabolic aberration(s) in primary gout. The results again indicate that some gouty subjects utilize glycine excessively in the biosynthesis of uric acid; others (the majority) give no indication of excessive incorporation of glycine into uric acid. The data in double-label isotope experiments suggest that this apparent difference in patients with primary gout may reflect different metabolic anomalies, although this point is not clearly established. In any event, analysis of the distribution of N^{15} and C^{14} in uric acid gives some clue to the general nature of the metabolic pathways which appear to be implicated, at least in gouty "hyperexcretors." These seem to be what are designated "alternative" pathways of purine biosynthesis, to differentiate them from the better established direct pathways for incorporation of intact glycine, which thus far have occupied the center of interest in considerations of the metabolic anomalies in gout.

Review

Dominance and Recessivity in Medical Genetics A. C. ALLISON AND B. S. BLUMBERG 933

The authors review the problem of dominance and recessivity in medical genetics. Dominant genes, in the original sense of the word, exert the same effect regardless of whether they are present in single or double dose. The present findings indicate that abnormal human genes have a more severe effect in double dose than in single dose. Fisher's theory of dominance modification by genes at other loci is shown to be applicable to man in relation to single dose expression of some human genes. Haldane's theory of selection of genes is reviewed also, and shown to be applicable to the nearly complete dominance of many normal human characters. Illustrative material is cited in lower animals, and several types of human disease, especially the hemoglobinopathies.

Seminar on the Brain

Present Status of the Schizophrenia Problem . . . . . EDWIN F. GILDEA 942

This symposium on the brain concludes appropriately with a consideration of the problem of schizophrenia, and Dr. Gildea has attempted in this brief article to summarize the present status. He has based his appraisal of this highly controversial and confused area largely upon the extensive review of the subject at the Second International Congress for Psychiatry held in 1957. The difficult problems of definition and hence of diagnosis are first considered; then the as yet disappointing attempts to find specific psychologic, physiologic or biochemical characteristics of schizophrenia that might serve as criteria for diagnosis and clues to etiology; finally, there is an evaluation of current methods of treatment.

Contents continued on page 9

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*Finnerty, F. A. Jr.: New York State J. Med. 57:2957 (Sept. 15) 1957.

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Clinico-pathologic Conference

Multiple Thrombotic Episodes with Death Following a Reaction to Miokon . . . 950

Clinico-pathologic Conference (Washington University School of Medicine).

Case Report

Hypogammaglobulinemia and Bronchial Asthma. Report of Two Cases in Adults
SAMUEL O. FREEDMAN, EARL B. BROWN AND PHYLLIS A. MYERS 961

While no cause-and-effect relationship between hypogammaglobulinemia and bronchial asthma can be said to have been established in the two cases described, the association is of interest and deserves further exploration.

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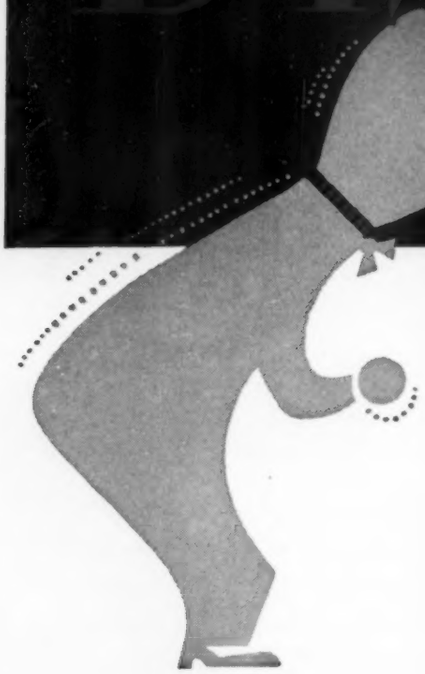
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Doshay, L.J., and Constable, K.: Treatment of Paralysis Agitans with Orphenadrine (Disipal) Hydrochloride: Results in One Hundred Seventy-Six Cases, J.A.M.A. *163*:1352 (Apr. 13) 1957.

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Finch, J.W.: Clinical Trial of Orphenadrine (Disipal) in Skeletal Muscle Disorders. Scientific Exhibit at Mississippi Valley Medical Society Meeting, St. Louis, Missouri, Sept. 3-5, 1957.



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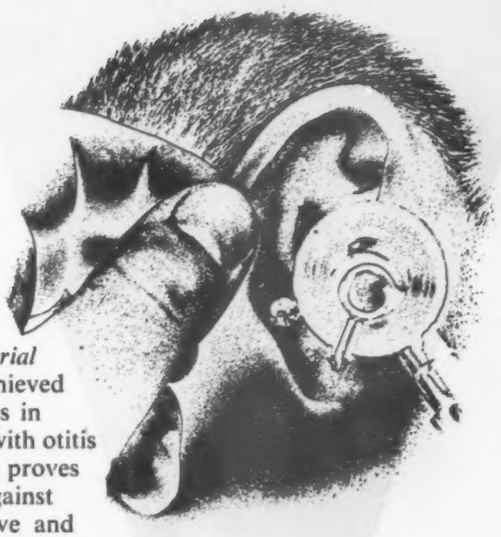
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1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958.
2. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958.
3. Robinson, H. M., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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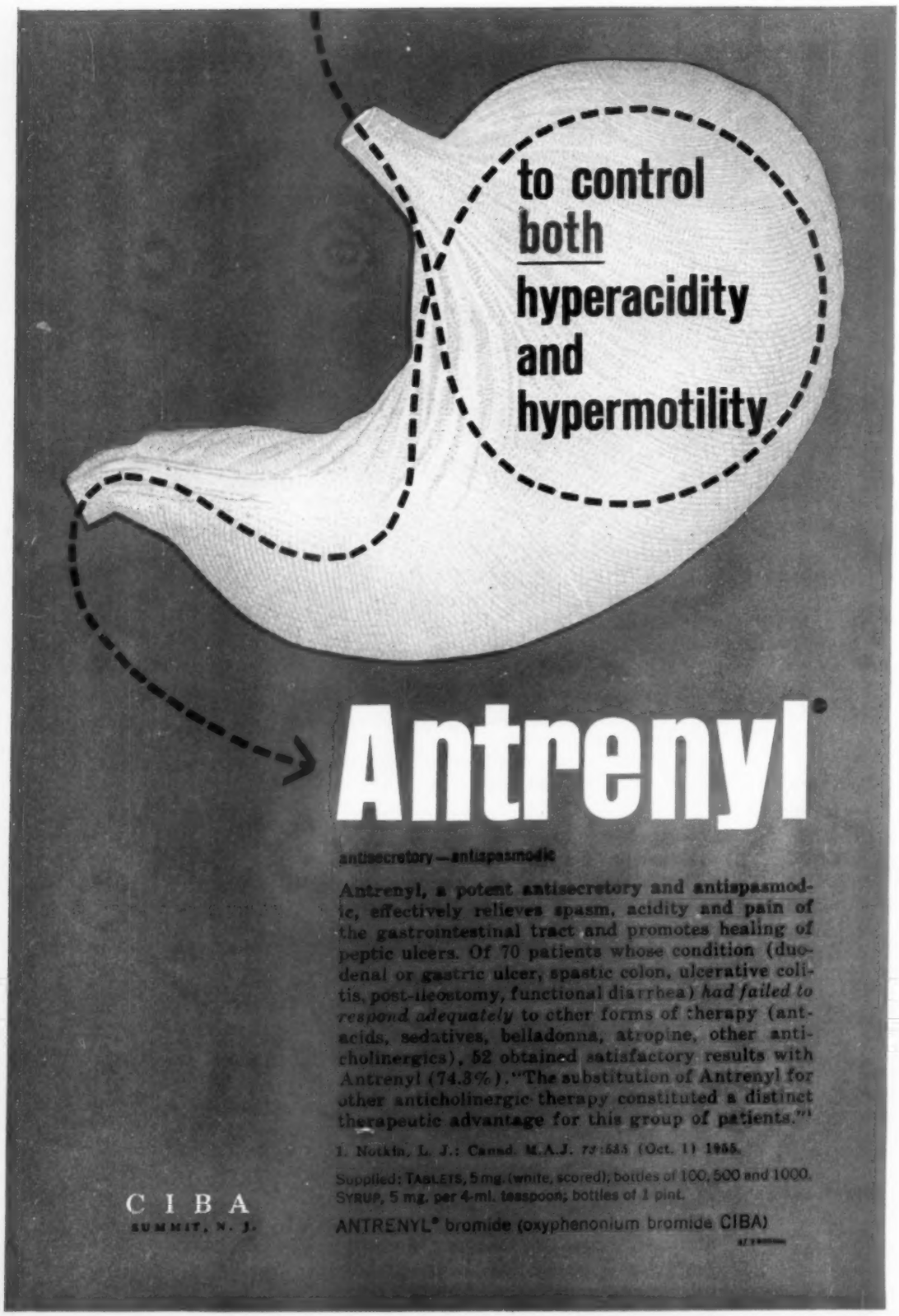
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References: 1. E. H. Townsend and A. Borgstedt, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

2. S. Ross, J. R. Puig and E. A. Zaremba, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

3. W. A. Leff, Paper read at the New Jersey Chapter of the American Federation for Clinical Research, East Orange, N. J., September 17, 1958.

4. W. P. Boger, Paper read at the Sixth Annual Symposium on Antibiotics, Washington, D.C., October 15-17, 1958.

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	40 lbs	1	½	2	1
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Caution: The usual precautions in sulfonamide therapy should be observed, including the maintenance of adequate fluid intake. If toxic reactions or blood dyscrasias occur, use of the drug should be discontinued. As is true of all sulfonamides, Madribon is probably contraindicated in premature infants.

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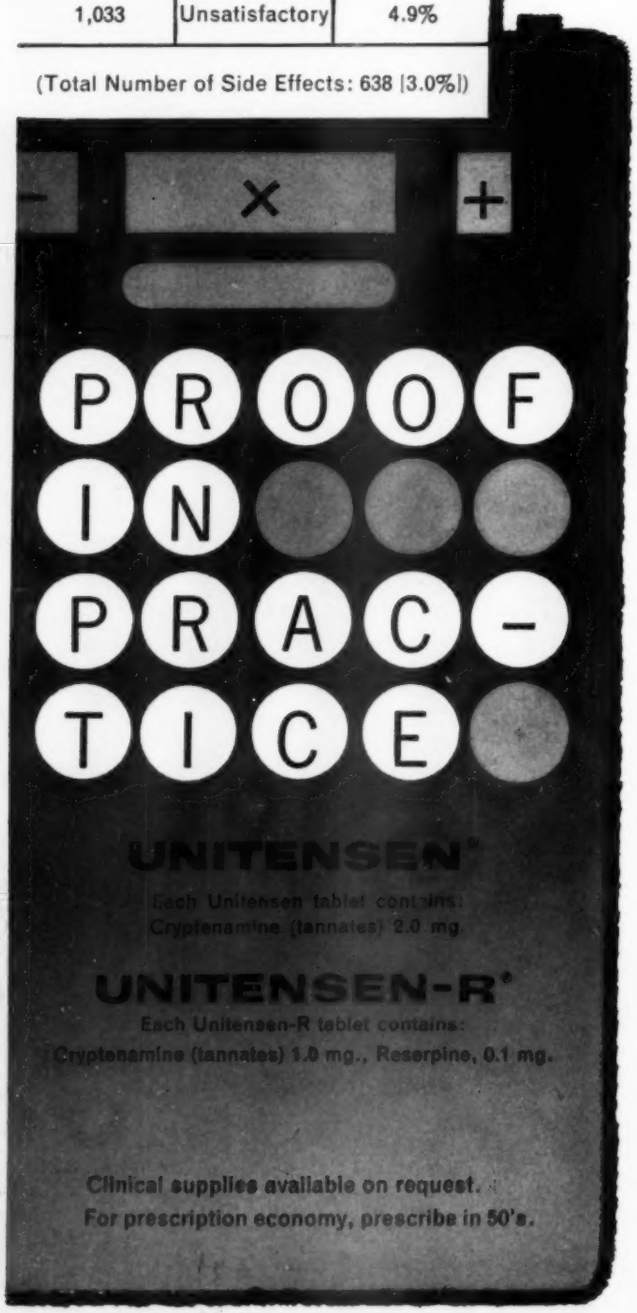
ROCHE—Reg. U. S. Pat. Off.

ROCHE LABORATORIES • *Division of Hoffmann-La Roche Inc* • *Nutley 10* • *N. J.*

SUMMARY OF REPORTS

No. of Patients	Results	Percent
6,553	Excellent	31.0%
10,843	Good	51.3%
2,703	Fair	12.8%
1,033	Unsatisfactory	4.9%

(Total Number of Side Effects: 638 [3.0%])

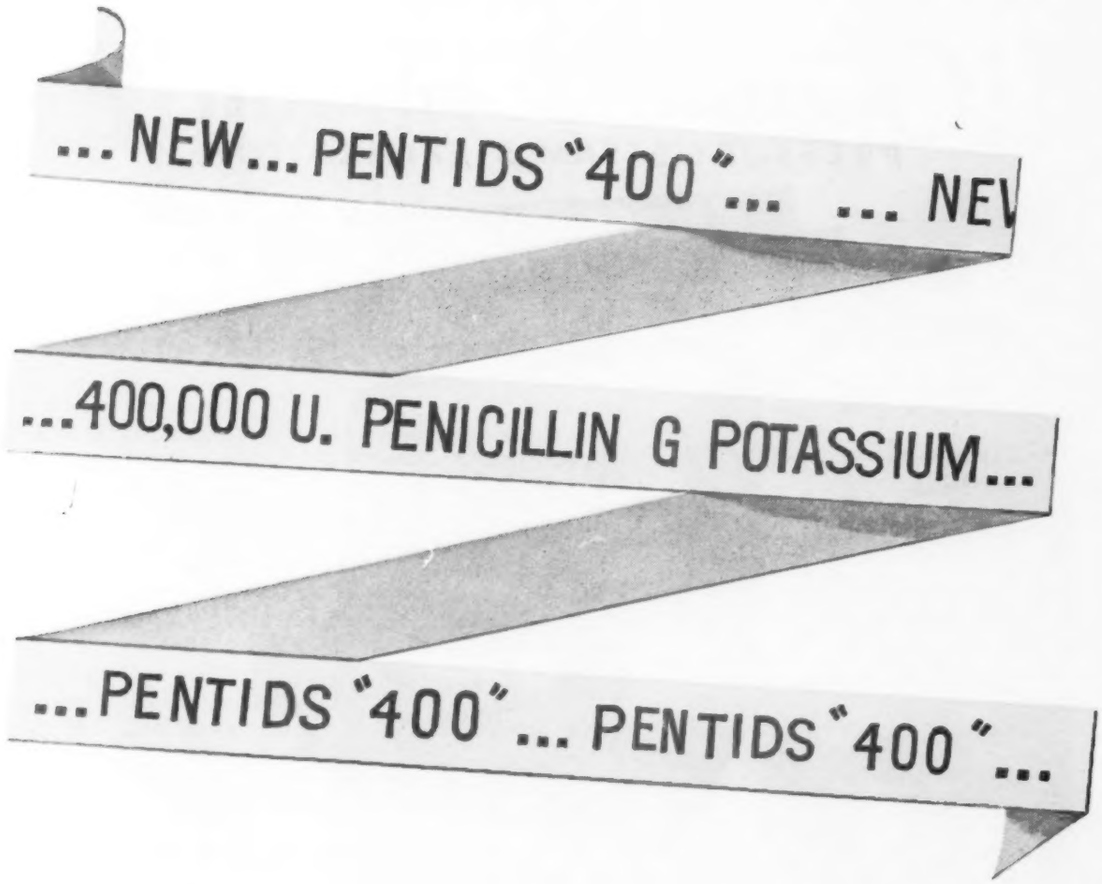


A NEW DIMENSION IN RESEARCH

This data deals with the results obtained by 1,988 physicians, treating 21,128 hypertensive patients with Unitensen. The "Proof In Practice" study validates, *in day-to-day private practice*, the findings of clinical trials conducted in hospitals and institutions. It proves that Unitensen affords safe, dependable office management for the majority of hypertensive patients. Unitensen lowers blood pressure . . . improves cerebral and renal blood flow... exerts no adverse effects on circulation . . . and, is virtually free of side effects.

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Irwin, Neisler & Co.
Decatur, Illinois



New convenient oral tablets . . . PENTIDS "400". . . Economical . . . where double strength Pentids is required for treatment of severe infections due to **Staphylococcus . . . Hemolytic Streptococcus . . . Pneumococcus.** Also indicated for prevention of streptococcal infections when there is a history of rheumatic fever. PENTIDS "400". . . Squibb Penicillin G Potassium 400,000 Unit Tablets (Buffered) . . . Dosage: 1 tablet t.i.d. without regard to meals . . . Supply: Scored tablets—bottles of 12 and 100.

For common bacterial infections, prescribe PENTIDS . . . 200,000 unit buffered Penicillin G Potassium Tablets . . . Dosage: 1 or 2 tablets t.i.d. without regard to meals . . . Supply: Scored tablets—bottles of 12 and 100.

PENTIDS® IS A SQUIBB TRADEMARK

Also available as . . .

Pentids for Syrup . . . Orange-flavored, provides 200,000 units Penicillin G Potassium per teaspoonful (5 cc.), 12 dose bottles . . . **Pentids Capsules** . . . each containing 200,000 units Penicillin G Potassium, bottles of 24 and 100 . . . **Pentids Soluble Tablets** . . . each containing 200,000 units Penicillin G Potassium, vials of 12 and bottles of 100 . . . **Pentids—Sulfas Tablets** . . . each containing 200,000 units Penicillin G Potassium with triple sulfas, bottles of 30 and 100.

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613-R PORTABLE DYNACLAVE



• The low cost, high performing American 613-R Dynaclave assures positive sterilization with pressure steam at 250°F. or 270°F. It is fast, reaching 270° F. in approximately seven minutes.

Operation is fully automatic with selective sterilizing cycles from 3 to 60 minutes. Cools and dries instruments or supplies by exhausting steam and residual water back into water reservoir—NOT into room.

The 613-R, with greater capacity, accommodates three large trays (6″ x 13″). Handsome, all stainless steel construction is durable and easy to clean. Other features include a Safety-Lock Door, Adjustable Thermostat and Accurate Temperature Gauge. Automatically burn-out proof.

See your authorized American Sterilizer dealer or write for Bulletin DC-410.

AMSCO

AMERICAN STERILIZER
Erie • Pennsylvania

IN CANADA: The American Sterilizer Company of Canada Limited, Brampton, Ontario

For dietary management of serum cholesterol..

Mazola® Corn Oil

...a natural food and the only readily available vegetable oil made from golden corn

...rich in important unsaturated fatty acids, contains 56% linoleic acid



EASY AND PLEASANT TO ADMINISTER

Mazola Corn Oil, a highly palatable natural food, can easily be included as part of the everyday meals...simply and without seriously disturbing the patient's usual eating habits.

EFFECTIVE

Extensive recent clinical findings now show that serum cholesterol levels tend to be lower when an adequate amount of Mazola Corn Oil is part of the daily meals... high levels are lowered...normal levels remain normal.

PREFERRED

Nutrition authorities commonly recommend that from one-third to one-half of the total fat intake should be of the unsaturated type, whenever serum cholesterol control is a problem. The high content of important unsaturated fatty acids in Mazola, plus its other desirable characteristics, make it the oil of choice.

UNMATCHED QUALITY

A superlative cooking oil, a delicious salad oil, clear, bland and odorless...adequate amounts of Mazola can be eaten daily as a natural food in a wide variety of salad dressings as well as in cooked, fried and baked foods.

Each TABLESPOONFUL of MAZOLA (14 Gm.)
Provides approximately:

LINOLEIC ACID	7.4 Gm.
Sitosterols	130 mg.
Natural tocopherols	15 mg.
Calories	126
Unsaturated fatty acids	85% of total

Prepared as a special service for Physicians by Corn Products Co.

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LATEST LITERATURE REVIEW

"Unsaturated Fats and Serum Cholesterol"

A comprehensive review of recent research findings and current concepts. This book covers the following subjects.

1. **The occurrence and behavior of cholesterol in the human body.**
2. **The effect of different dietary fats on serum cholesterol levels.**
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new round-the-clock therapeutic effect

GRADUMET®

TRAL®

for the peptic ulcer patient

Gradual, Metered Release The new Gradumet makes a therapeutic amount of drug quickly available to the patient... releases the remainder slowly, smoothly over the next 8 to 12 hours. The GRADUMET employs no enteric coatings, wax-fat wrappings or series of layers.

Smoother, More Constant Release Rate Because the TRAL in the GRADUMET is immediately exposed to the patient's gastrointestinal fluids, changes in gastric acidity... altered intestinal motility... or increased enzymatic activity cannot speed up or slow down either the GRADUMET release rate or the absorption of the TRAL.

Complete Drug Absorption The GRADUMET is made with its thousands of pores of exactly the right size to provide an 8- to 12-hour release period for the TRAL. At the end of this time, all the TRAL has been released from the GRADUMET and absorbed by the patient. Only the empty, inert matrix of the GRADUMET remains, to be excreted later in the stool.



Full Symptomatic Relief Thus, with the new GRADUMET TRAL, the peptic ulcer patient obtains true round-the-clock anticholinergic effect . . . still with a minimum of undesirable side effects. GRADUMET TRAL 50 mg., and GRADUMET TRAL 50 mg. with Phenobarbital 30 mg., are supplied at pharmacies everywhere in bottles of 50 and 500.

Abbott

® GRADUMET—LONG-RELEASE DOSE FORM, ABBOTT; PATENT APPLIED FOR.
® TRAL—HEXOCYCLIUM METHYLSULFATE, ABBOTT. 811162

MORE EFFICIENT THAN PREDNI-STEROIDS ALONE

ATARAXOID®

prednisolone-hydroxyzine

'TOTAL PATIENT' THERAPY



EFFECTIVELY CONTROLS anxiety-tension-induced exacerbations and emotional factors through the safe tranquilizer and muscle-relaxant[1] effects of hydroxyzine. Potentiates the action of prednisolone, markedly improving degree of response, sometimes doubling dosage efficiency, and permitting lower dosages.[2-4] The unique antisecretory action[5] of hydroxyzine also minimizes corticoid-induced gastric reactions.

1. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind.
2. Johnston, T. G., and Casort, A. G.: Clin. Rev. 1:17, 1958.
3. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957.
4. Individual Case Reports to Medical Dept., Pfizer Laboratories.
5. Strub, I. H.: To be published.

SUPPLIED:

ATARAXOID *5.0*
scored green tablets, 5.0 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 30 and 100.

ATARAXOID *2.5*
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scored orchid tablets, 1.0 mg. prednisolone and 10 mg. hydroxyzine hydrochloride, bottles of 100.

Pfizer

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which women...

and when...

need

iron therapy?



Many clinicians agree that the normal woman of child-bearing age requires iron therapy for a month or six weeks of *each* year.

Iron-deficiency anemia, usually identified as hypochromic microcytic anemia, is seen in most age groups, from the adolescent to the senior members.

For the treatment of these common anemias, Livitamin offers *peptonized* iron—virtually predigested, well absorbed, and less irritating than other forms. The Livitamin formula, which contains the B complex, provides integrated therapy to normalize the blood picture.

Formula: Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

LIVITAMIN®

with Peptonized Iron

The S. E. MASSENGILL Company BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

To ensure desired therapeutic response — look to peptonized iron



CURRENT STUDIES* SHOW PEPTONIZED IRON

One-third as toxic as ferrous sulfate.

Absorbed as well as ferrous sulfate.

Non-astringent.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

More rapid response in iron-deficient anemias.

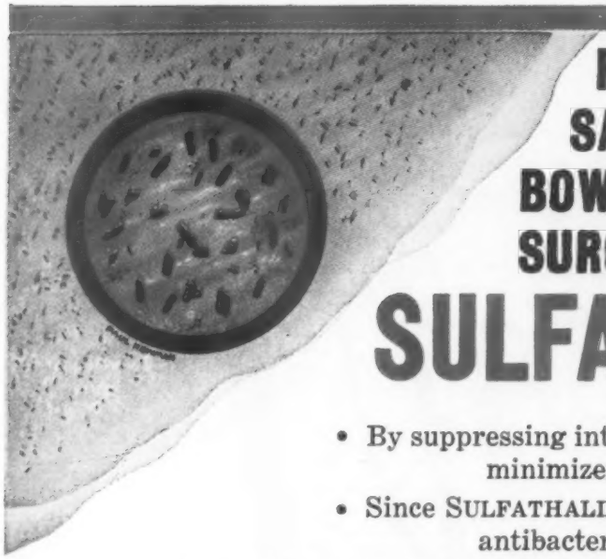
*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

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FOR SAFER BOWEL SURGERY

SULFATHALIDINE®

PHTHALYLSULFATHIAZOLE

- By suppressing intestinal pathogens, SULFATHALIDINE minimizes a major danger in bowel surgery.
- Since SULFATHALIDINE is virtually nonabsorbable, its antibacterial effect is concentrated in the gut.
- SULFATHALIDINE has specific value as an adjunct in ulcerative colitis.

Available as 0.5 Gm. tablets in bottles of 100 and 1000—also as CREMOTHALIDINE®, a palatable suspension of SULFATHALIDINE. Each 30 cc. (1 fluidounce) contains 6.0 Gm. SULFATHALIDINE.

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EQUANITRATE*

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Meprobamate and Pentaerythritol Tetranitrate

Tablets, vials of 50, meprobamate (200 mg.) and pentaerythritol tetranitrate (10 mg.)

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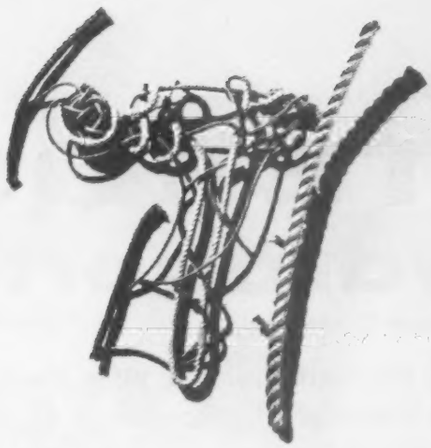
PYELONEPHRITIS

"A DISEASE OF THE TUBULES"[1] AS WELL AS THE GLOMERULI

In pyelonephritis, "the tubules suffer from damage to their lining cells which show cloudy swelling, granular degeneration and diminution in size. Inflammatory cells and colloid casts are found in the lumen of the tubules. Inflammatory cells are present also in the interstitial tissue. The glomeruli remain normal over a long period."[1]

FURADANTIN®

brand of nitrofurantoin



In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

In the treatment of pyelonephritis, it is important to select an agent such as Furadantin which—in addition to its glomerular filtration—is secreted by the tubule cells. On the other hand, it has been demonstrated that sulfonamides, both free and acetylated, are excreted primarily by glomerular filtration,[2] and that "the mechanism of excretion of tetracycline is solely a glomerular filtration process without tubular involvement."[3]

In pyelonephritis . . . FURADANTIN, first

Furadantin "may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants. The importance of an agent with these characteristics that could be used for a long period in the treatment of chronic pyelonephritis has been recognized, and it is in this sphere that nitrofurantoin may have its greatest use."[4]

Available as Tablets, Oral Suspension

References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955.



NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

outstanding efficacy in **skin disorders**

STEROSAN®
Hydrocortisone

Cream and Ointment (chlorquinaldol GEIGY with hydrocortisone)

The case illustrated below typifies the superior response produced by STEROSAN-Hydrocortisone. Combining potent antibacterial-antifungal action with a reliable anti-inflammatory and antipruritic effect, STEROSAN-Hydrocortisone is valuable in a wider range of infective or allergic dermatoses.

A severe infectious eczematoid dermatitis on foot of 15-year-old boy. Patient used STEROSAN-Hydrocortisone preparation 3 times a day for 23 days with a dramatic improvement as shown.*



before treatment



after treatment

*Case report and photographs through the courtesy of N. Orentreich, M.D., New York, N.Y.

STEROSAN®-Hydrocortisone (3% chlorquinaldol GEIGY with 1% hydrocortisone) Cream and Ointment. Tubes of 5 Gm. Prescription only.

GEIGY ARDSLEY, NEW YORK

for depression

▲Deprol▲†

Clinically confirmed in over 2,500 documented case histories[1,2]

CONFIRMED EFFICACY

Deprol ► acts promptly to control depression *without* stimulation

► restores natural sleep

► reduces depressive rumination and crying

DOCUMENTED SAFETY

Deprol is unlike amine-oxidase inhibitors

► does not adversely affect blood pressure or sexual function

► causes no excessive elation

► produces no liver toxicity

► does not interfere with other drug therapies

Deprol is unlike central nervous stimulants

► does not cause insomnia

► produces no amphetamine-like jitteriness

► does not depress appetite

► has no depression-producing aftereffects

► can be used freely in hypertension and in unstable personalities

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each tablet contains 400 mg. meprobamate and 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl).

Supplied: Bottles of 50 scored tablets.

1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.

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ED-7491

Literature and samples on request WALLACE LABORATORIES, *New Brunswick, N.J.*



HIGHLY EFFECTIVE AGAINST STAPHYLOCOCCI...

CHLOROMYCETIN®

Reports on studies of *in vitro* activity of CHLOROMYCETIN over the past few years indicate that this antibiotic has maintained its effectiveness against most strains of staphylococci.[1-4] "...Staphylococci do not acquire resistance to chloramphenicol [CHLOROMYCETIN] as they do to other antibiotics, in spite of heavy use of chloramphenicol [CHLOROMYCETIN]."[1]

These *in vitro* studies are borne out by excellent clinical results with CHLOROMYCETIN in treatment of patients for severe staphylococcal infections, including staphylococcal pneumonia,[5] postoperative wound infections,[6] postoperative parotitis,[7] and puerperal breast abscesses.[8]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

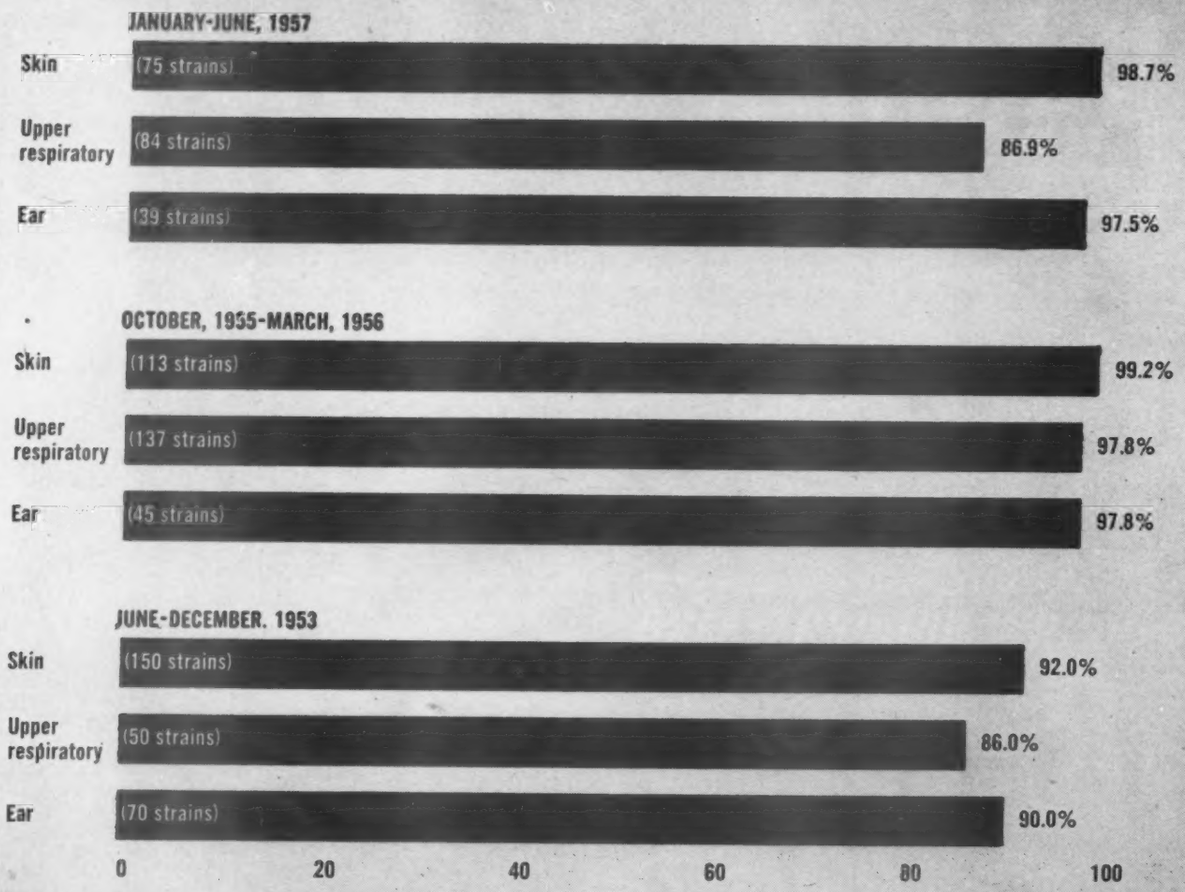
CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Royer, A., in Welch, H., & Martí-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 783. (2) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* **101**:397, 1958. (3) Koch, R., & Donnell, G.: *California Med.* **87**:313, 1957. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* **77**:844, 1957. (5) Cooper, M. L., & Keller, H. M.: *J. Dis. Child.* **95**:245, 1958. (6) Caswell, H. T., *et al.*: *Surg., Gynec. & Obst.* **106**:1, 1958. (7) Brown, J. V.; Sedwitz, J. L., & Hanner, J. M.: *U. S. Armed Forces M. J.*: **9**:161, 1958. (8) Sarason, E. L., & Bauman, S.: *Surg., Gynec. & Obst.* **105**:224, 1957.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN



IN VITRO SENSITIVITY OF STAPHYLOCOCCI FROM THREE FOCI OF INFECTION TO CHLOROMYCETIN FROM 1953 TO 1957*



*Adapted from Royer.[1]

36258

- postoperatively
- in pregnancy when vomiting is persistent
- following neurosurgical diagnostic procedures
- in infections, intra-abdominal disease, and carcinomatosis
- after nitrogen mustard therapy

for nausea and vomiting

VESPRIN

Squibb Triflupromazine

- provides prompt, potent, and long-lasting control
- capable of depressing the gag reflex
- effective in cases refractory to other potent antiemetic agents
- may be given intravenously, intramuscularly and orally
- no pain or irritation on injection

ANTIEMETIC DOSAGE:
Intravenous: 8 mg. average single dose
Dosage range 2-10 mg.
Intramuscular: 15 mg. average single dose
Dosage range 5-15 mg.
If subsequent parenteral dose is needed, one-half the original dose will usually suffice
Oral: 10-20 mg. initially; then 10 mg. t.i.d.

SUPPLY:
Parenteral solution – 1 cc. ampuls (20mg./cc.)
Oral tablets – 10 mg., 25 mg., 50 mg., in bottles of 50 and 500

SQUIBB *Squibb Quality – The Priceless Ingredient*

"VESPRIN" ® IS A SQUIBB TRADEMARK

THE ORINASE EPOCH

BREAKTHROUGH IN DIABETES

Upjohn

*TRADEMARK, REG. U.S. PAT. OFF. — TOLBUTAMIDE — UPJOHN



Location of the clinical and research centers throughout the United States where thousands of investigators helped to make possible the advent of

ORINASE

BREAKTHROUGH IN DIABETES

Just last year, a new chapter began in the treatment of diabetes: Orinase became available for general clinical practice. Today, more than 300,000 diabetics are enjoying the advantages of oral management. This extensive experience, reinforcing the findings of hundreds of investigators in research centers all over the United States, has confirmed that Orinase is both safe and effective in the majority of adult, stable diabetics. And we now know that the significance of Orinase goes even further.

Before Orinase, research in diabetes was moving ahead slowly. Pathogenesis of the disease remained an enigma, and the mechanism of insulin action continued to elude investigators. Nor was any explanation forthcoming for the different types of diabetes mellitus, the progressive nature of the disease, or for the wide range of insulin requirements.

Clinically, too, there was much to be desired: the lifelong regimen of daily injections, the rigid meal schedules, and, above all, the constant threat of hypoglycemia. To the patient, these meant a life centered around his disease; to the physician, the ever-present danger of complications.

And now, one year after the introduction of Orinase, what has experience taught us? What has Orinase meant to practicing physicians, to patients, to investigators? What can we expect of the future? In briefest summary, this is where the evidence points:

1 **Diabetes mellitus does not appear to be a single pathological entity.** There are several types of diabetes mellitus. The most common is **"Orinase-positive"** diabetes, in which administration of Orinase induces release and utilization of the patient's endogenous insulin.

2 **In "Orinase-positive" diabetics, Orinase achieves better control** than injections of exogenous insulin.

Facts and Figures

ORINASE

ONE YEAR AGO–1957

Orinase was officially released for prescription on June 3, 1957. Prior to its release, it had been thoroughly and painstakingly tested in more than 20,000 patients.

NUMBER OF PATIENTS ON ORINASE:	20,000
CRITERIA OF PATIENT SELECTION:	Adult, stable diabetes (onset around 40 years of age)
INCIDENCE OF SIDE EFFECTS: *(transitory skin rash, nausea, etc.)*	Only 3%
TOXICITY:	None
ESSENTIAL CONDITION FOR RESPONSE TO ORINASE:	Functional pancreas
PRIMARY MODE OF ACTION OF ORINASE:	Unknown
CONTRAINDICATIONS:	Juvenile diabetes…brittle diabetes…history of coma, acidosis, or ketosis…fever… severe trauma…gangrene…diabetes adequately controlled by diet alone.

ONE YEAR LATER–1958

Today, Orinase is a routine therapeutic agent in the management of hundreds of thousands of diabetics. Numerous clinical observations confirm its efficacy and have brought to light many new, additional benefits of Orinase therapy.

Over 300,000
Age: 40+ (at onset) Insulin: 40–(daily requirements) *These are typical criteria for the candidate most likely to respond to Orinase. However, diabetics with an earlier development of the disease also deserve a careful trial with Orinase, because Orinase has been found effective in many of the 20 to 40 age-of-onset diabetics.*
Approximately 3% (side effects continue to be mild and transitory–drug withdrawn for these effects in only 1.6%)
None
Functional beta cells of the pancreas
In the presence of a functional pancreas, Orinase effects the production and utilization of *native* insulin via *normal* channels.
Juvenile diabetes…brittle diabetes…history of coma, acidosis, or ketosis…fever…severe trauma…gangrene…diabetes adequately controlled by dietary restriction alone.

Objective advantages of Orinase

Intensive diabetic research, stimulated by the introduction of Orinase, has led many investigators to revise the very concept of diabetes as a single clinical entity, and to coin the term *"Orinase-positive"* diabetes. Oral therapy of *"Orinase-positive"* diabetics presents the following advantages:

Better control of diabetes

Orinase-responsive patients show more stable blood sugar levels and less glycosuria on Orinase than on insulin. Because Orinase acts via *endogenous* insulin, daily control of diabetes is smoother; "peaks and valleys" typical of exogenous insulin are leveled out.

Greater freedom from hypoglycemia

Patients on Orinase rarely experience hypoglycemic reactions. Even when hypoglycemia does occur, it is milder and more amenable to therapy than insulin (hypoglycemic) reactions.

Side effects—few and minor

Side effects attributable to Orinase occur in about 3% of cases, and only half of these necessitate withdrawal of Orinase. Most common are skin rashes or mild G. I. upsets.

No known toxicity

Careful observations of large series of patients maintained on Orinase for more than two years revealed no damage to the liver, blood, kidneys, or pancreas. Orinase is not goitrogenic.

Painless management of diabetes

Simple, easy, oral administration eliminates subcutaneous fat atrophy and frequent allergic reactions to insulin.

No increase in insulin requirements

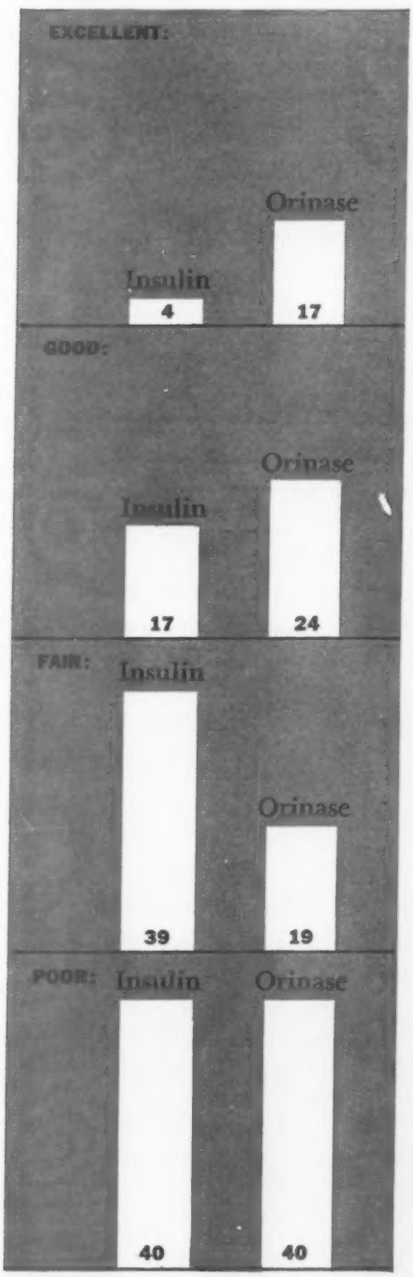
Even after prolonged Orinase therapy, patients scarcely ever show any increase in insulin requirements. In fact, such increase on Orinase is *less common than on insulin.*

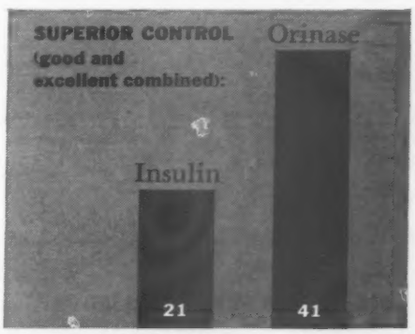
No impairment of diabetic status

Orinase therapy does not aggravate the underlying diabetic pathology. In some cases, there may be an actual improvement or even a remission.

QUALITY OF DIABETIC CONTROL IN 100 PATIENTS ON ORINASE COMPARED WITH CONTROL ON INSULIN[1]

Control rating:



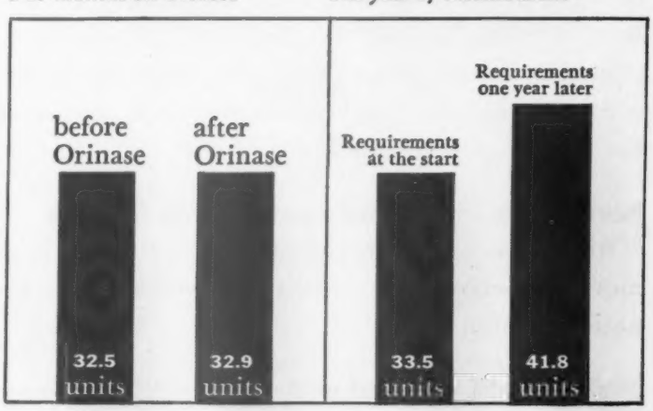


BETTER CONTROL OF DIABETES WITH ORINASE

NO INCREASE IN INSULIN REQUIREMENTS ON ORINASE[2]

Change in average insulin requirements of 30 diabetics resuming insulin after 1-15 months on Orinase

Change in average insulin requirements of 100 diabetics after one year of insulin alone



1. Based on the data of McKendry, J. B. R.; Kuwayti, K., and Sagle, L. A.: Canad. M. A. J. 77:429 (Sept. 1) 1957.
2. Based on the data of Pfeiffer, E. F.: J. Endocrinol. 15:xlviii (June) 1957.

Subjective advantages of Orinase

"The extreme satisfaction of patients whose conditions are now controlled with tolubutamide is immeasurable."

Breneman, J. C.: J.A.M.A. *164*:627 (June 8) 1957.

ORINASE HELPS TO CORRECT MAJOR DISLOCATIONS IN THE LIFE PATTERN OF DIABETICS

Orinase tends to restore emotional balance

Diagnosis of diabetes, usually coming late in life and carrying with it a long sentence of daily fear and anxiety, profoundly upsets the emotional balance of the average patient. Adjustment to radical changes in daily living is difficult. Daily injections, special meal schedules, and new limitations on activities make the patient feel "set apart." Oral therapy simplifies life, brings it closer to normal, helps restore a cheerful, hopeful outlook.

Sense of personal freedom regained on Orinase

No longer tied to a refrigerator, sterilizing apparatus, nearest restaurant, and rigid schedules, a diabetic on Orinase can enjoy travel and a variety of personal activities, free from the tyranny of the clock and the threat of hypoglycemia.

Orinase makes diabetes easier on the patient's family

With no dependence on members of the family for diabetic care, the patient can resume a more normal place in the family circle.

Orinase permits occupational continuity

Because of the hazards of hypoglycemic shock, some diabetics are forced to give up their customary occupations, or must limit and curtail their working hours—as may be the case with traveling salesmen, business executives, and others with unpredictable work schedules. On Orinase, patients usually can continue their normal occupations.

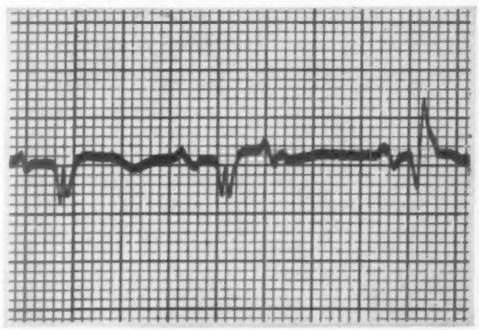
Normal social life made possible by Orinase

"Orinase-positive" diabetics can visit their friends, without the embarrassing necessity of meals at special hours...can participate in community life and social events in a more normal fashion.

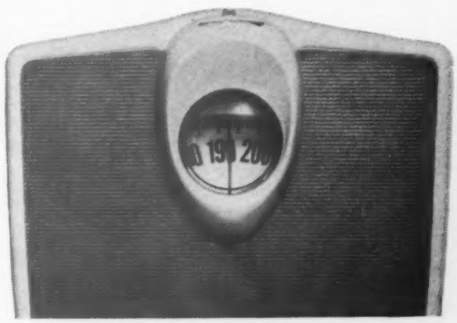
Stability and sense of well-being on Orinase

Patients report an increased sense of stability and well-being...they are less irritable...their mood and outlook are improved.

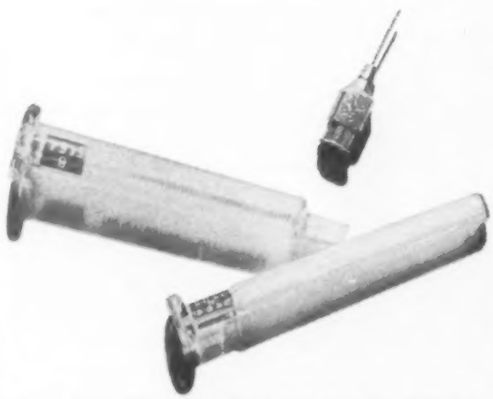
ADDED ADVANTAGES OF ORINASE IN DIABETICS WITH SPECIAL PROBLEMS



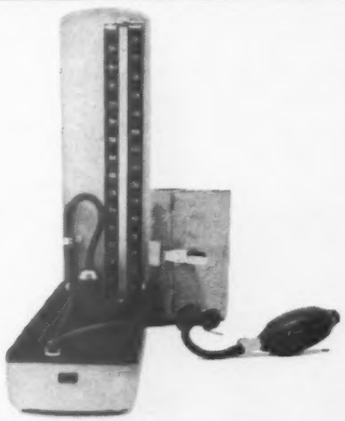
IN THE DIABETIC WITH CARDIOVASCULAR COMPLICATIONS, Orinase helps avoid superimposed hypoglycemic stress



IN THE OBESE DIABETIC, Orinase helps reinforce dietary discipline



IN THE DIABETIC WITH FEAR OF INJECTIONS, Orinase affords greater equanimity through oral control



IN THE DIABETIC WITH HYPERTENSION, Orinase reduces the pressure of rigid schedules



IN THE DIABETIC WITH TREMOR, Orinase overcomes the possibility of inaccurate self-injection



IN THE DIABETIC WITH IRREGULAR WORKING HOURS, Orinase removes the "tyranny of the clock" from the patient's therapeutic regimen

A New Life in THE ORINASE EPOCH

J.D.—FEMALE—AGE 32

Jane D., a successful commercial artist, now 32 years of age, had a sudden onset of diabetes in her early twenties after going through what seemed an

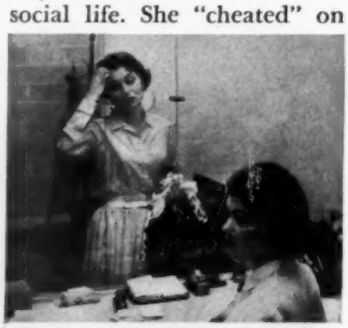


unduly prolonged and difficult recovery from a severe infection. At that time, she also experienced concomitant emotional upsets. When the diagnosis of diabetes was confirmed by a fasting blood sugar of 230 mg. per 100 cc. and 4 plus sugar in the urine, Jane was placed on 40 units of NPH insulin in the morning, and 5 units at night to prevent noc-



turnal hyperglycemia. She was ordered to maintain a restricted diet. Good control was established after a few hypoglycemic episodes secondary to disruption of her meal schedule.

When she returned to her drawing board after her illness and began her diabetic regimen, Jane found that her ability to function was impaired. She "felt ashamed" of her diabetes and refused to discuss it with anyone. She described herself as "limited emotionally" in both her business and social life. She "cheated" on



her diet and suffered accordingly, physically and psychologically. Because her work as an artist required her to conform to demands of clients for business meetings at odd hours and to complete assignments on rigid deadlines, she found herself under increasingly severe tensions. These, and her somewhat exaggerated fears of possible hypoglycemic reactions, carried over into her social activities as well.

The transfer to Orinase

Ten months ago, Jane's physician successfully transferred her from insulin to oral control with Orinase, establishing excellent balance on 0.5 Gm. t.i.d. Although she had become inured to her insulin injections, she found other factors in the oral medication providing definite advantages: less effort; emotional release from many of her former fears and tensions; greater freedom to work on irregular schedules; and ability to confront possible disruption of her mealtime.

Jane D. now leads a more normal existence. She is able to work consistently despite her irregular schedule. She is more relaxed in all her activities, and finds that her "consciousness of diabetes" has been virtually eliminated.

This case, illustrating some of the changing aspects of diabetes control offered by oral management, is based on actual clinical data.



THE ORINASE EPOCH

BREAKTHROUGH FOR THE PATIENT

A more normal, more secure life for the majority of diabetics.

BREAKTHROUGH FOR THE PHYSICIAN

Smoother control, free from the danger of hypoglycemic shock.

BREAKTHROUGH FOR METABOLIC INVESTIGATORS

New stimulus and new evidence in searching for the final answers to diabetes.

Dosage: Patients responsive to Orinase may begin therapy as follows:

First day . . . . . 3 Gm.
Second day . . . . . 2 Gm.
Third day . . . . . 1 Gm.

Usual maintenance dose . . . . . 1 Gm.
(must be adjusted to patient's response)

To change from insulin to Orinase:
If previous insulin dosage was less than

40 u./day reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

more than 40 u./day reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

Prior to using Orinase in selected patients, the physician should perform a complete physical examination and indicated laboratory studies. During the initial test period, the patient should report to the physician daily, and for the first month at least once weekly for physical examination and blood sugar determination. After the first month, the patient should be examined at monthly intervals or more frequently as indicated.

The patient should be instructed to report immediately to his physician if he does not feel as well as usual.

It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failures of treatment.

Supplied: In 0.5 Gm. scored tablets, bottles of 50.

Upjohn

The Upjohn Company
Kalamazoo, Michigan

ORINASE®

*TRADEMARK, REG. U.S. PAT. OFF. FOR TOLBUTAMIDE, UPJOHN

PRINTED IN U.S.A.

ACHROCIDIN*

TETRACYCLINE-ANTIHISTAMINE-ANALGESIC COMPOUND LEDERLE

A versatile, well-balanced formula for treating common upper respiratory infections, particularly during respiratory epidemics; when bacterial complications are observed or are likely; when patient's history is positive for recurrent otitic, pulmonary, nephritic, or rheumatic involvement.

CHECKS SYMPTOMS: Includes traditional components for rapid relief of the traditional nonspecific nasopharyngitis, symptoms of malaise, chilly sensations, inconstant low-grade fever, headache, muscular pain, pharyngeal and nasal discharge.

Available on prescription only.

Adult dosage for ACHROCIDIN Tablets and new caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children according to weight and age.

TABLETS *(sugar coated)*
Each Tablet contains:

ACHROMYCIN® Tetracycline	125 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Salicylamide	150 mg.
Chlorothen Citrate	25 mg.

Bottles of 24 and 100.

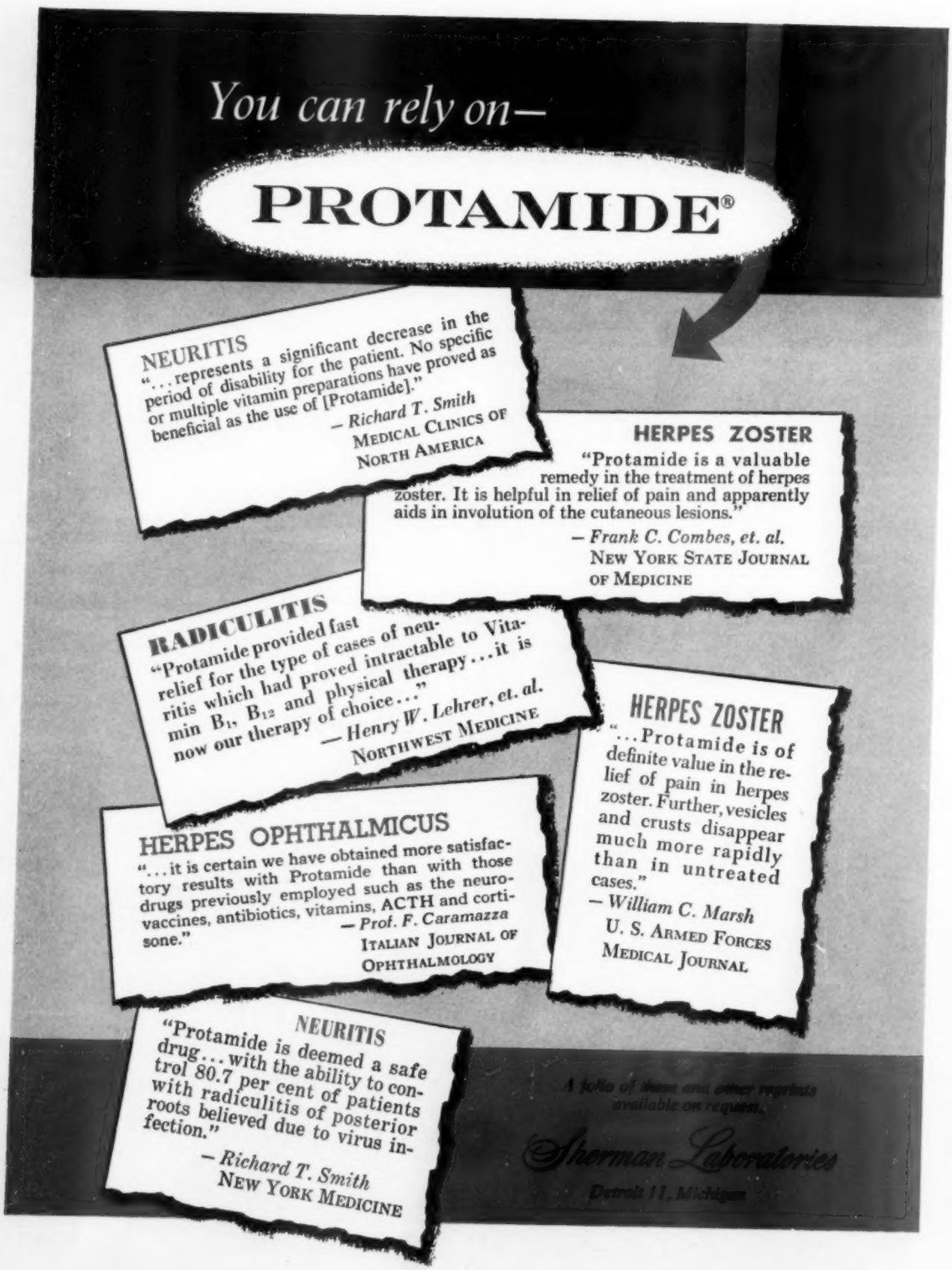
SYRUP *(lemon-lime flavored)*
Each teaspoonful (5 cc.) contains:

ACHROMYCIN® Tetracycline equivalent to tetracycline HCl	125 mg.
Phenacetin	120 mg.
Salicylamide	150 mg.
Ascorbic Acid (C)	25 mg.
Pyrilamine Maleate	15 mg.
Methylparaben	4 mg.
Propylparaben	1 mg.

Bottle of 4 oz.



Lederle **LEDERLE LABORATORIES**, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York
*Reg. U.S. Pat. Off.


You can rely on—
PROTAMIDE®
NEURITIS
"...represents a significant decrease in the period of disability for the patient. No specific or multiple vitamin preparations have proved as beneficial as the use of [Protamide]."
— Richard T. Smith
MEDICAL CLINICS OF NORTH AMERICA
HERPES ZOSTER
"Protamide is a valuable remedy in the treatment of herpes zoster. It is helpful in relief of pain and apparently aids in involution of the cutaneous lesions."
— Frank C. Combes, et. al.
NEW YORK STATE JOURNAL OF MEDICINE
RADICULITIS
"Protamide provided fast relief for the type of cases of neuritis which had proved intractable to Vitamin B1, B12 and physical therapy... it is now our therapy of choice..."
— Henry W. Lehrer, et. al.
NORTHWEST MEDICINE
HERPES OPHTHALMICUS
"...it is certain we have obtained more satisfactory results with Protamide than with those drugs previously employed such as the neurovaccines, antibiotics, vitamins, ACTH and cortisone."
— Prof. F. Caramazza
ITALIAN JOURNAL OF OPHTHALMOLOGY
HERPES ZOSTER
"...Protamide is of definite value in the relief of pain in herpes zoster. Further, vesicles and crusts disappear much more rapidly than in untreated cases."
— William C. Marsh
U. S. ARMED FORCES MEDICAL JOURNAL
NEURITIS
"Protamide is deemed a safe drug...with the ability to control 80.7 per cent of patients with radiculitis of posterior roots believed due to virus infection."
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NEW YORK MEDICINE
A folio of these and other reprints available on request.
Sherman Laboratories
Detroit 11, Michigan

This patient's blood-pressure controlled for the first time without side effects

Remember this particular patient. He typifies the thousands of patients involved in a clinical investigation which promises to bring about a major change in rauwolfia therapy. The patient is being treated in a Massachusetts hospital. His blood pressure without treatment ranged up to 220/138; now *for the first time,* it is being maintained near normal *without side effects.* This dramatic case history is part of the story of a remarkable new antihypertensive agent **Singoserp**™
(syrosingopine CIBA)

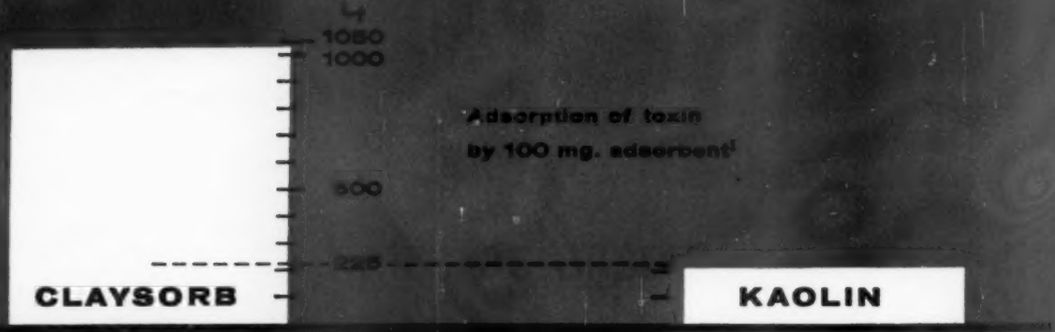
coming as soon as sufficient supplies are available...
from CIBA, *world leader in hypertension research.*

2/260BMK



In diarrhea . . .

adsorptive power



CLAYSORB is 5 times as adsorptive as kaolin

When you prescribe POLYMAGMA or POLYMAGMA Plain to control diarrhea, you are prescribing adsorptive superiority. Both preparations contain Claysorb—a new intestinal adsorbent whose superiority over kaolin has been demonstrated in exhaustive studies.[1,2,3]

For *bacterial* diarrhea, POLYMAGMA is bactericidal to many intestinal pathogens. It is soothing and protective to the irritated mucosa. It aids in the restoration of normal intestinal function. Highly effective, highly palatable.

For *nonbacterial* diarrhea, POLYMAGMA Plain—same formula but without antibiotics.

1. Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) *46*:493 (Aug.) 1957. 2. Barr, M., and Arnista, E.S.: *Ibid.* *46*:486 (Aug.) 1957. 3. Barr, M.: *Ibid.* *46*:490 (Aug.) 1957.

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

*Trademark

Wyeth®
Philadelphia 1, Pa.

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.





"flooding the limbs with blood ...is a prime objective"[1]

in **intermittent claudication**

of **arteriosclerosis obliterans**
thromboangiitis obliterans
diabetic vascular disease

...also effective in **Raynaud's syndrome**
ischemic ulcers
night leg cramps

arlidin®

brand of nylidrin hydrochloride N.N.R.

Sends comforting, fresh blood where blood is needed most —to distressed muscles.[1-5] Tissue oxygenation and nutrition, and muscle metabolism are improved, spasm relaxed, pain relieved.

Arlidin is available in 6 mg. scored tablets, and 5 mg. per cc. parenteral solution. See PDR for dosage and packaging.

Protected by U.S. Patent Numbers 2,661,372 and 2,661,373

Samples and literature[1-5]

arlington-funk laboratories
division of **U. S. VITAMIN CORPORATION**
250 East 43rd Street, New York 17, N. Y.

to relieve edema of

DIURIL®"

CHLOROTHIAZIDE

FINNERTY, F. A., Buchholz, J. H. and Tuckman, J.: J.A.M.A. **166**:141, Jan. 11, 1958.

DIURIL (Chlorothiazide) given alone to 85 patients, ". . . caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria. . . . The average effective dose was found to be 1 Gm. per day by mouth. . . . The usually excellent response coupled with the absence of significant toxicity and lack of development of drug resistance makes chlorothiazide ideal for the prevention and treatment of toxemia."

DOSAGE: one or two 500 mg. tablets of DIURIL once or twice a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide); bottles of 100 and 1,000.

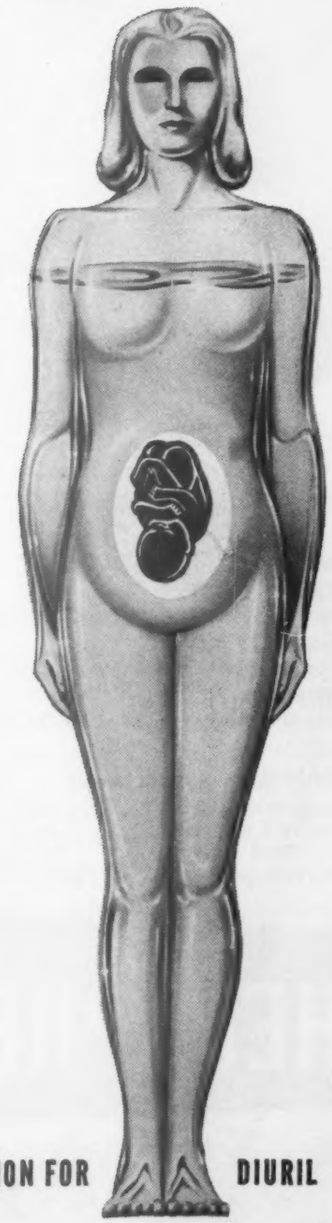
DIURIL is a trademark of Merck & Co., Inc.

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MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa. MSD

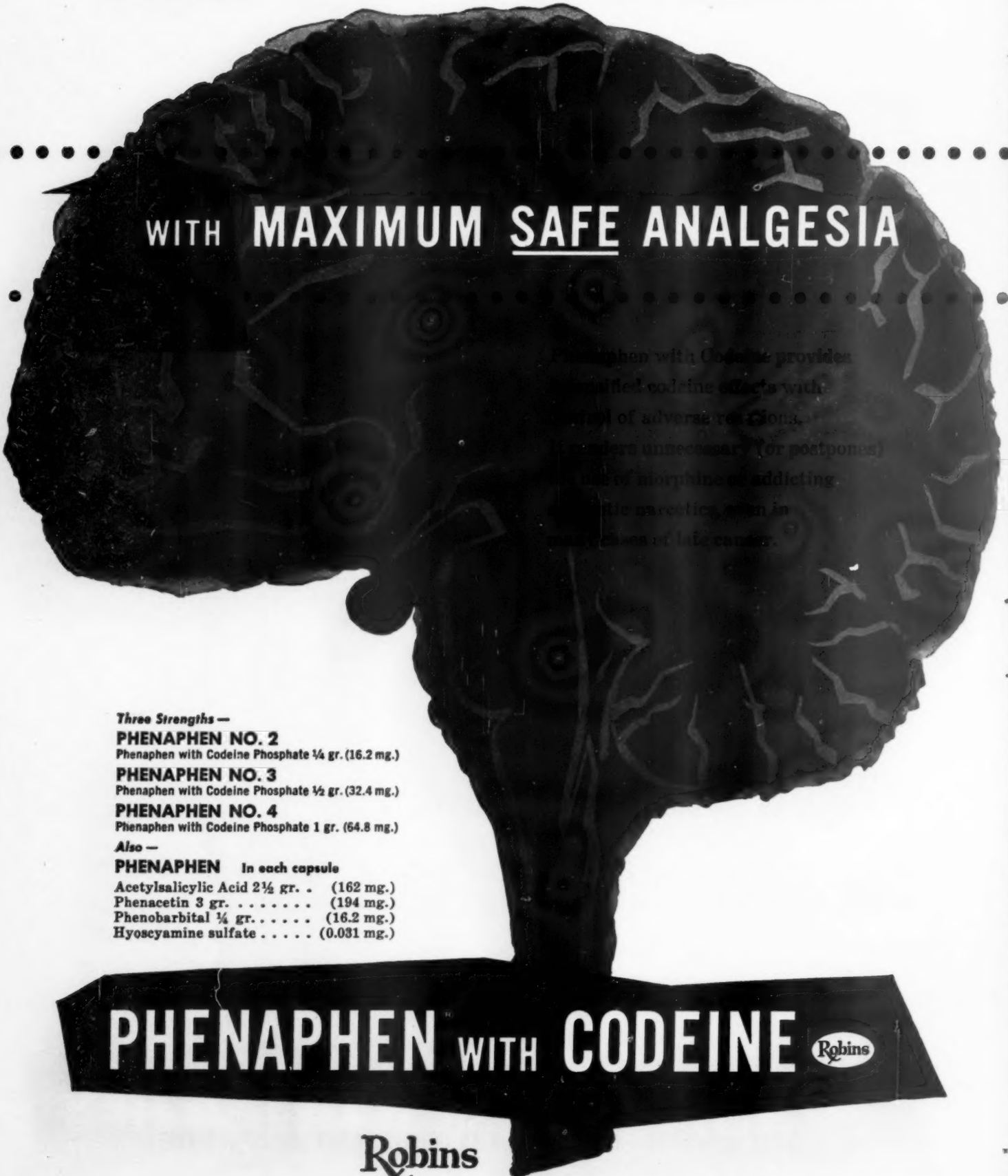
pregnancy

....caused an excellent diuresis, with reduction of edema, weight, blood pressure, and albuminuria...."



ANY INDICATION FOR DIURESIS IS AN INDICATION FOR DIURIL

Raise the Pain Threshold



WITH MAXIMUM SAFE ANALGESIA

Three Strengths —

PHENAPHEN NO. 2
Phenaphen with Codeine Phosphate ¼ gr. (16.2 mg.)

PHENAPHEN NO. 3
Phenaphen with Codeine Phosphate ½ gr. (32.4 mg.)

PHENAPHEN NO. 4
Phenaphen with Codeine Phosphate 1 gr. (64.8 mg.)

Also —

PHENAPHEN In each capsule

Acetylsalicylic Acid 2½ gr. . (162 mg.)
Phenacetin 3 gr. . . . . (194 mg.)
Phenobarbital ¼ gr. . . . . (16.2 mg.)
Hyoscyamine sulfate . . . . . (0.031 mg.)

PHENAPHEN WITH CODEINE

Robins

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878



Localizing accumulated radioiodine in thyroid remnants with the 6 mm needle probe to assure complete thyroidectomy.

New Versatile Nuclear-Chicago Beta-Gamma Scintillation Probe



Needle probes are provided in these sizes:
2 mm x 10 cm (2.5 mil stainless steel wall)
3 mm x 10 cm (2.5 mil nickel wall)
6 mm x 15 cm (2.5 mil nickel wall)
All probes are easily interchanged by loosening and tightening a simple hand nut.

Designed for the surgeon, radiotherapist or gynecologist, the new Nuclear-Chicago Model DS8 Scintillation Detector is ideal for application in brain tumor localization, pinpointing radioisotope concentrations in thyroid or neoplastic tissue, and estimating radiation doses in radiotherapy. The detector, with three unique, interchangeable needle probes, is a compactly-designed, convenient, lightweight instrument with the complete reliability and accuracy so essential to medical applications.

This rugged detector weighs less than 5 ounces and is only one inch in diameter. It can be sterilized in solutions commonly used in the operating room, is corrosion-proof, and its quality components provide practically infinite life. The beta-gamma sensitive crystals are mounted in the needles in such a way that the active volume is confined to the very tip of the probes.

For more than 12 years we have been designing and manufacturing for the medical profession high quality instrumentation for detecting and measuring radioactivity. We will be pleased to provide you with full information on the Model DS8 Scintillation Probe and on other Nuclear-Chicago instruments for clinical use.

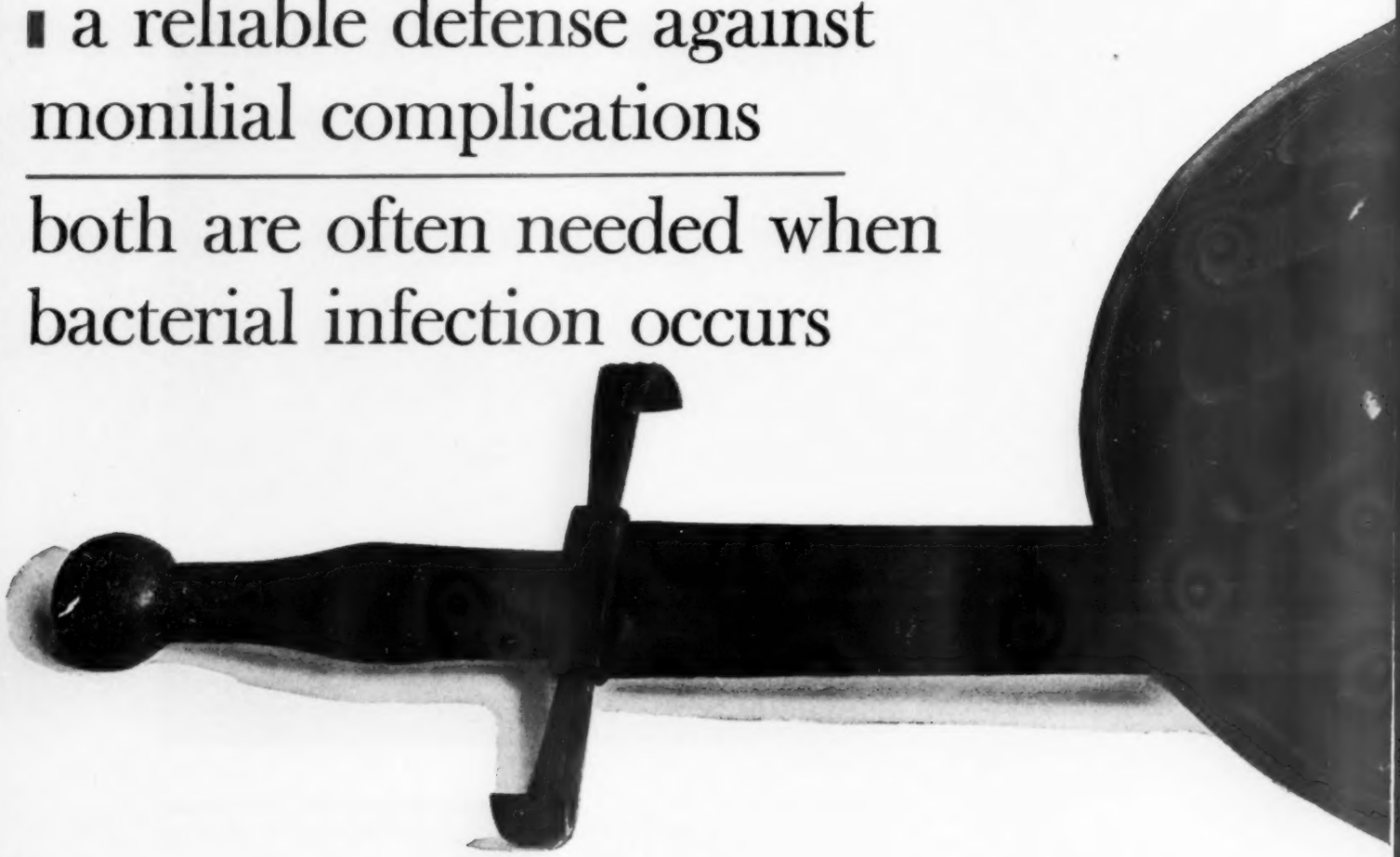
Radioisotopes are creating new frontiers in medicine

nuclear-chicago
CORPORATION
253 WEST ERIE STREET · CHICAGO 10, ILLINOIS

▮ prompt, aggressive antibiotic action

▮ a reliable defense against monilial complications

both are often needed when bacterial infection occurs



for a direct strike at infection Mysteclin-V contains tetracycline phosphate complex

It provides a direct strike at all tetracycline-susceptible organisms (most pathogenic bacteria, certain rickettsias, certain large viruses, and Endamoeba histolytica).

It provides the new chemical form of the world's most widely prescribed broad spectrum antibiotic.

It provides unsurpassed initial blood levels—higher and faster than older forms of tetracycline—for the most rapid transport of the antibiotic to the site of infection.

'MYSTECLIN'®, 'SUMYCIN'® AND 'MYCOSTATIN'® ARE SQUIBB TRADEMARKS

SQUIBB CENTENNIAL 1858 III 1958 SQUIBB

Squibb Quality—the Priceless Ingredient

Capsules *(250 mg./250,000 u.), bottles of 16 and 100.*
Half-strength Capsules *(125 mg./125,000 u.), bottles of 16 and 100.*
Suspension *(125 mg./125,000 u. per 5 cc.) 60 cc. bottles.*
Pediatric Drops *(100 mg./100,000 u. per cc.). 10 cc. dropper bottles.*



for protection against monilial complications
Mysteclin-V contains Mycostatin

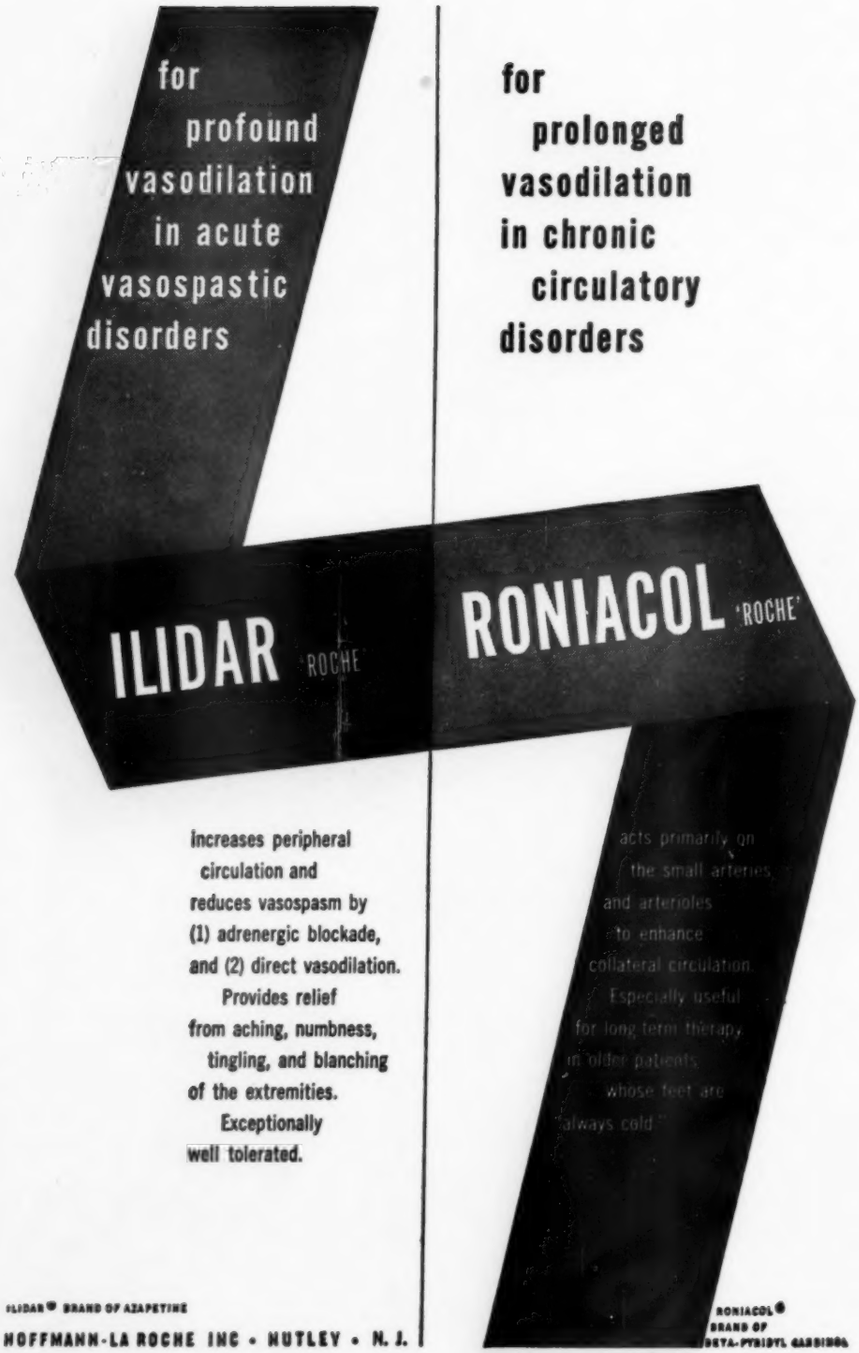
It provides the antifungal antibiotic, first tested and clinically confirmed by Squibb, with specific action against Candida (Monilia) albicans.

It acts to prevent the monilial overgrowth which frequently occurs whenever tetracycline or any other broad spectrum antibiotic is used.

It protects your patient against antibiotic-induced intestinal moniliasis and its complications, including vaginal and anogenital moniliasis, even potentially fatal systemic moniliasis.

MYSTECLIN-V

Squibb Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)


for profound vasodilation in acute vasospastic disorders
for prolonged vasodilation in chronic circulatory disorders
ILIDAR ROCHE
RONIACOL 'ROCHE'
increases peripheral circulation and reduces vasospasm by (1) adrenergic blockade, and (2) direct vasodilation.
Provides relief from aching, numbness, tingling, and blanching of the extremities.
Exceptionally well tolerated.
acts primarily on the small arteries and arterioles to enhance collateral circulation.
Especially useful for long term therapy in older patients whose feet are always cold.
ILIDAR® BRAND OF AZAPETINE
HOFFMANN-LA ROCHE INC • NUTLEY • N. J.
RONIACOL® BRAND OF BETA-PYRIDYL CARBINOL

PAIN Zactirin®

Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation[1,2,3] in 1998 patients in diverse areas of medicine and surgery, including:

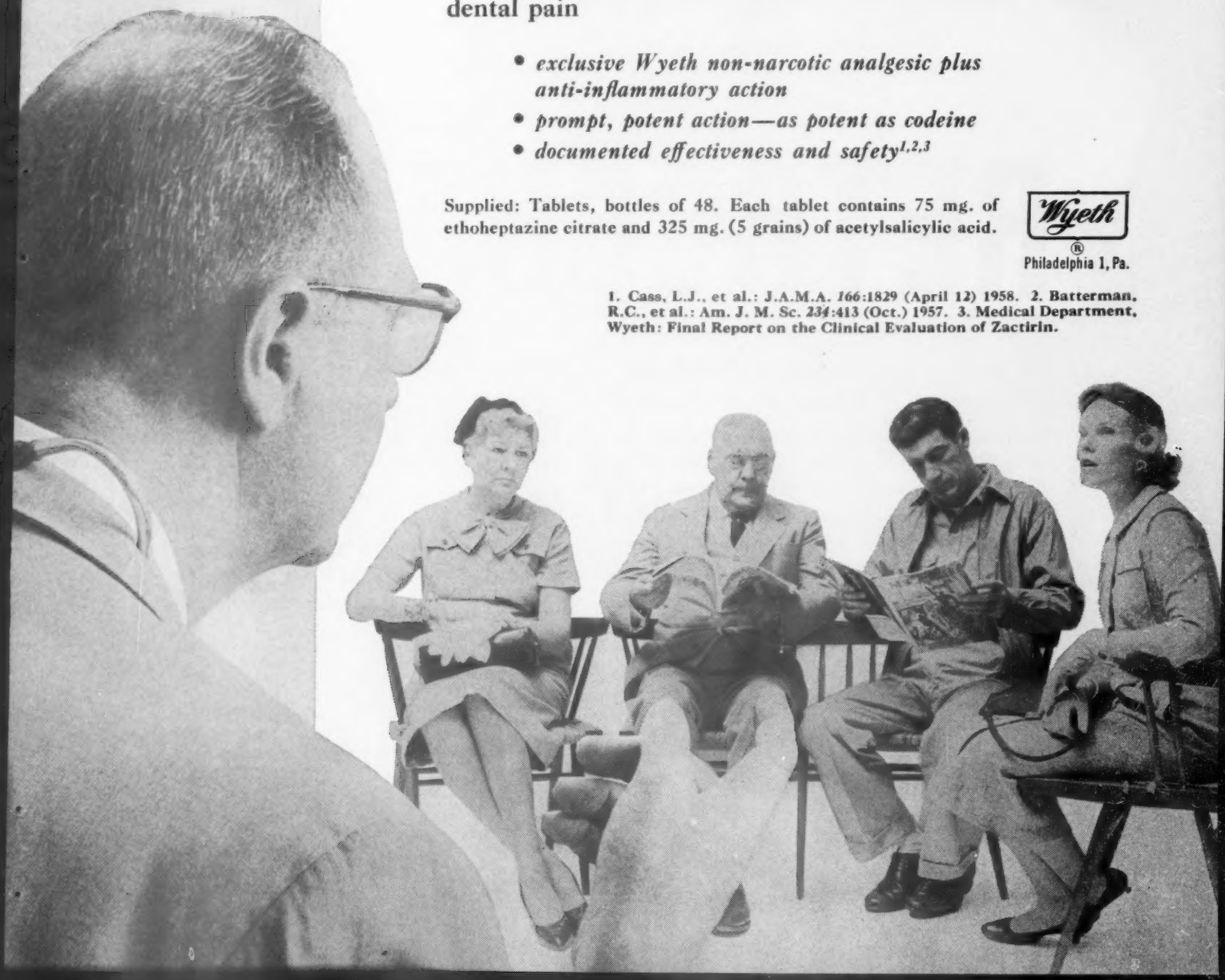
arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

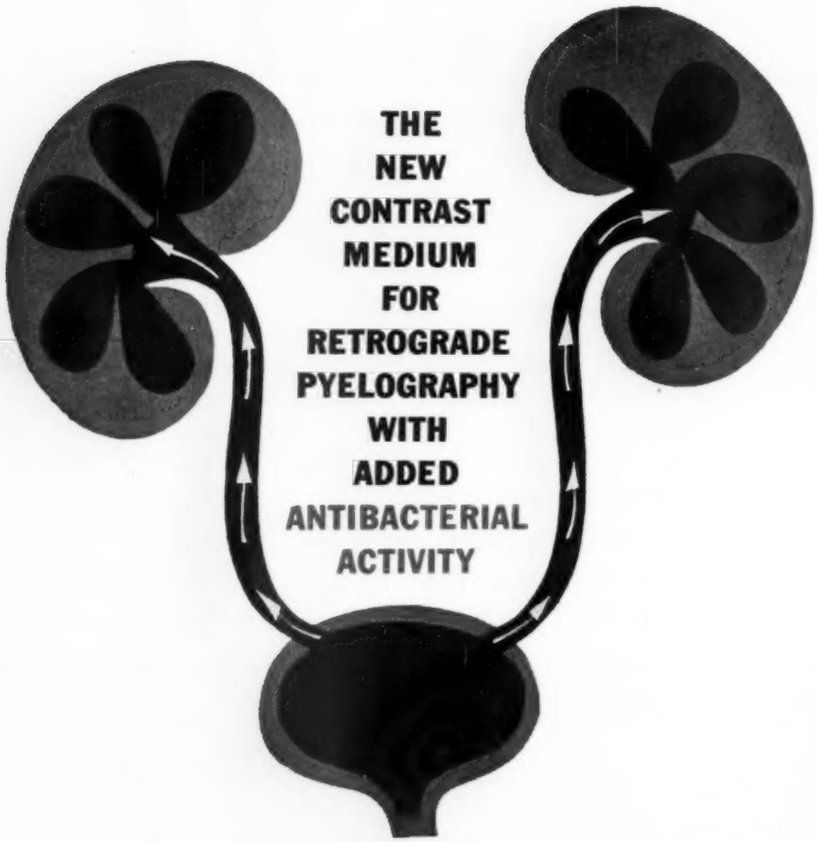
- *exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action*
- *prompt, potent action—as potent as codeine*
- *documented effectiveness and safety[1,2,3]*

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

Wyeth®
Philadelphia 1, Pa.

1. Cass, L.J., et al.: J.A.M.A. *166*:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc. *234*:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.





RETROGRAFIN

Squibb Sodium and Methylglucamine Diatrizoates and Neomycin Sulfate

for maximum opacification when urinary tract infection is present or suspected

Retrografin provides the same excellent film quality... exceptional patient toleration... and optimal convenience in retrograde pyelography as that provided by Renografin 30%. *And,* in addition, it contains 2½% neomycin (as the sulfate) for widely effective bactericidal action in cases with proved or suspected urinary tract infection. *Supplied in 50 cc. vials*

Retrograde pyelography with either Retrografin or Renografin 30% is especially useful when poor kidney function makes other procedures impractical, or when retrograde study will provide supplemental diagnostic information.

for routine retrograde pyelography

RENOGRAFIN 30%

Squibb Sodium and Methylglucamine Diatrizoates

Its excellent local tissue tolerance and proved systemic tolerance, even in the presence of pyelo-renal backflow, make Renografin 30% the preferred agent for routine, optimal density retrograde pyelograms. *Supplied in 50 cc. vials*

SQUIBB CENTENNIAL 1858 1958 SQUIBB

Squibb Quality—the Priceless Ingredient

'RETROGRAFIN' AND 'RENOGRAFIN'® ARE SQUIBB TRADEMARKS

ANNOUNCING

a new order of magnitude in corticosteroid therapy!

The great corticosteroid era
opened ten years ago
with the introduction of CORTONE® (cortisone).
Today, MERCK SHARP & DOHME proudly
presents the crowning
achievement of the first corticosteroid
decade—DECADRON (dexamethasone)
—a new and unique compound, which
brings a new order of magnitude
to corticosteroid therapy



Decadron

DEXAMETHASONE

to treat more patients more effectively

MSD MERCK SHARP & DOHME

a new order of magnitude

In Anti-Inflammatory Potency

DECADRON "possesses greater anti-inflammatory potency per milligram than any steroid yet produced,"[1] and is "the most potent steroid thus far synthesized."[2] Milligram for milligram, it is, on the average, 5 times more potent than 6-methylprednisolone or triamcinolone; 7 times more potent than prednisone; 28 times more potent than hydrocortisone; and 35 times more potent than cortisone.

In Dosage Reduction

Thanks to this unprecedented potency, DECADRON is "highly effective in suppressing the manifestations of rheumatoid arthritis when administered in remarkably small daily milligram doses."[3] In a number of cases, doses as low as 0.5-0.8 mg. proved sufficient for daily maintenance. The average maintenance dosage in rheumatoid arthritis is about 1.5 mg. daily.

In Elimination and Reduction of Side Effects

Virtual absence of diabetogenic activity, edema, sodium or water retention, hypertension, or psychic reactions has been noted with DECADRON.[1,2,3,4] Other "classical" reactions were less frequent and less severe. DECADRON showed no increase in ulcerogenic potential, and digestive complaints were rare. Nor have there been any new or "peculiar" side effects, such as muscle wasting, leg cramps, weakness, depression, anorexia, weight loss, headache, dizziness, tachycardia or erythema. Thus DECADRON introduces a new order of magnitude in safety, unprecedented in corticosteroid therapy.

In Therapeutic Effectiveness

With DECADRON, investigators note "a decided intensification of the anti-inflammatory activity"[3] and antirheumatic potency.[4] Clinically, this was manifested by a higher degree of improvement in many patients, previously treated with prednisteroids,[3] and by achievement of satisfactory control in an impressive number of recalcitrant cases.[3,4]

In Therapeutic Range

More patients can be treated more effectively with DECADRON. Its higher anti-inflammatory potency frequently brings relief to cases resistant to other steroids. Virtual freedom from diabetogenic effect in therapeutic dosage permits treatment of many diabetics without an increase in insulin requirements. Absence of hypertension and of sodium and fluid retention allows effective therapy of many patients with cardiovascular disorders. Reduction in the incidence and severity of many side effects extends the benefits of therapy to numerous patients who could not tolerate other steroids. And a healthy sense of well-being, reported by nearly all patients on DECADRON, assures greater patient cooperation.

References:

1. Boland, E.W.: California Med. 88:417 (June) 1958.
2. Bunim, J.J., et al.: Arthr. & Rheum. 1:313 (Aug.) 1958.
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"Penicillinase [Neutrapen] should be given as soon as possible after onset of symptoms."[5]
(M. C. Zimmerman—Antibiotics Annual, 1957-58)

- effective in 97% of cases[1]
- acts within an hour, lasts up to a week[2,3]
- one injection sufficient in 80% of cases[1]
- itching abates promptly[4]
- most reactions clear in 12 to 96 hours[1,5]
- well tolerated[1-9]
- may be lifesaving in certain anaphylactoid reactions[6,7]



Obscure sources—even cases with no history of penicillin therapy respond to NEUTRAPEN if the reaction has been caused by penicillin from sources such as milk, Roquefort or Bleu cheese, or penicillin-containing vaccines.[1,5,9]

NEUTRAPEN—800,000 units I. M.—should be given as soon as symptoms appear. May be repeated on the third day if response is not satisfactory. In anaphylactic reactions, epinephrine should be given and other supportive measures should be instituted immediately, followed by 800,000 units of NEUTRAPEN I. V. and 800,000 units I. M.

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References: (1) Zimmerman, M. C.: Clin. Med. *5*:305, 1958. (2) Becker, R. M.: New England J. Med. *254*:952, 1956. (3) Chen, J. Y. P.; Bard, J. W., and Balsito, A. A., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 321. (4) Minno, A. M., and Davis, G. M.: J.A.M.A. *165*:222 (Sept. 21), 1957. (5) Zimmerman, M. C., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 312. (6) Becker, R. M.: Ann. Int. Med. *48*:1228, 1958. (7) Becker, R. M., in Welch, H., and Marti-Ibañez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 310. (8) Davis, G. M.: Discussion, Antibiotics Symposium, Washington, D. C., October 3, 1957. (9) Zimmerman, M. C.: J.A.M.A. *167*:1807 (Aug. 9), 1958.

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SchenLabs SCHENLABS PHARMACEUTICALS, INC., NEW YORK 1, N. Y.

Exactly how does new Halodrin* restore the "premenopausal prime" in postmenopausal women?

Webster defines "prime" as the period of greatest health, strength, and beauty. In a woman, these are the childbearing years between puberty and menopause—the years when her hormone production is highest.

The inevitable reduction in this hormone production as she enters the menopause often results in physical discomfort in the form of hot flushes, nervousness, insomnia, or a multiplicity of other symptoms with which you are familiar. Superimposed on this physical picture is the psychic trauma brought on by this unavoidable evidence of aging. The thing that brings her to a physician is simply that she "feels bad."

You can't make her 35 again—but the odds are good that you can make her feel like it! The secret is a combination of reassurance and hormones. The exact form and amount of the former defy objective analysis, but the latter can now be provided with scientific precision. Reduced to essentials, here is the explanation of exactly how hormones—in the form of Upjohn's new Halodrin—restore the "premenopausal prime."

The normal premenopausal woman excretes estrogens in the urine in the form of estradiol, estrone, and estriol, in an approximate 28-day average ratio of 39:15:46. Starting with this urinary excretion of estrogens, it is possible to calculate backwards and estimate the amount of estradiol that must have been secreted endogenously in order to produce these urinary levels. This is possible because the proportion of estrogens which appears in the urine following parenteral administration has been established in castrated women.

On this basis, the average endogenous output of estrogens is about 160 micrograms per day during a menstrual cycle, and 80 micrograms per day in postmenopausal women (see chart opposite). Therefore, the restoration of the "premenopausal prime" in the postmenopausal woman requires the replacement of approximately the equivalent of the 80 micrograms of estradiol per day that she no longer secretes endogenously.

Oral ethinyl estradiol is about 2 to 2½ times as potent as parenteral estradiol. Therefore, the replacement of 80 micrograms of endogenous estradiol production per day is accomplished by the oral administration of 32 to 40 micrograms of ethinyl estradiol per day.

Each Halodrin tablet contains 20 micrograms of ethinyl estradiol, which means that the recommended dosage of 2 tablets per day provides 40 micrograms of ethinyl estradiol. This offsets the loss of 80 micrograms of endogenous estradiol production in the menopausal woman; i.e., restores the "premenopausal prime."

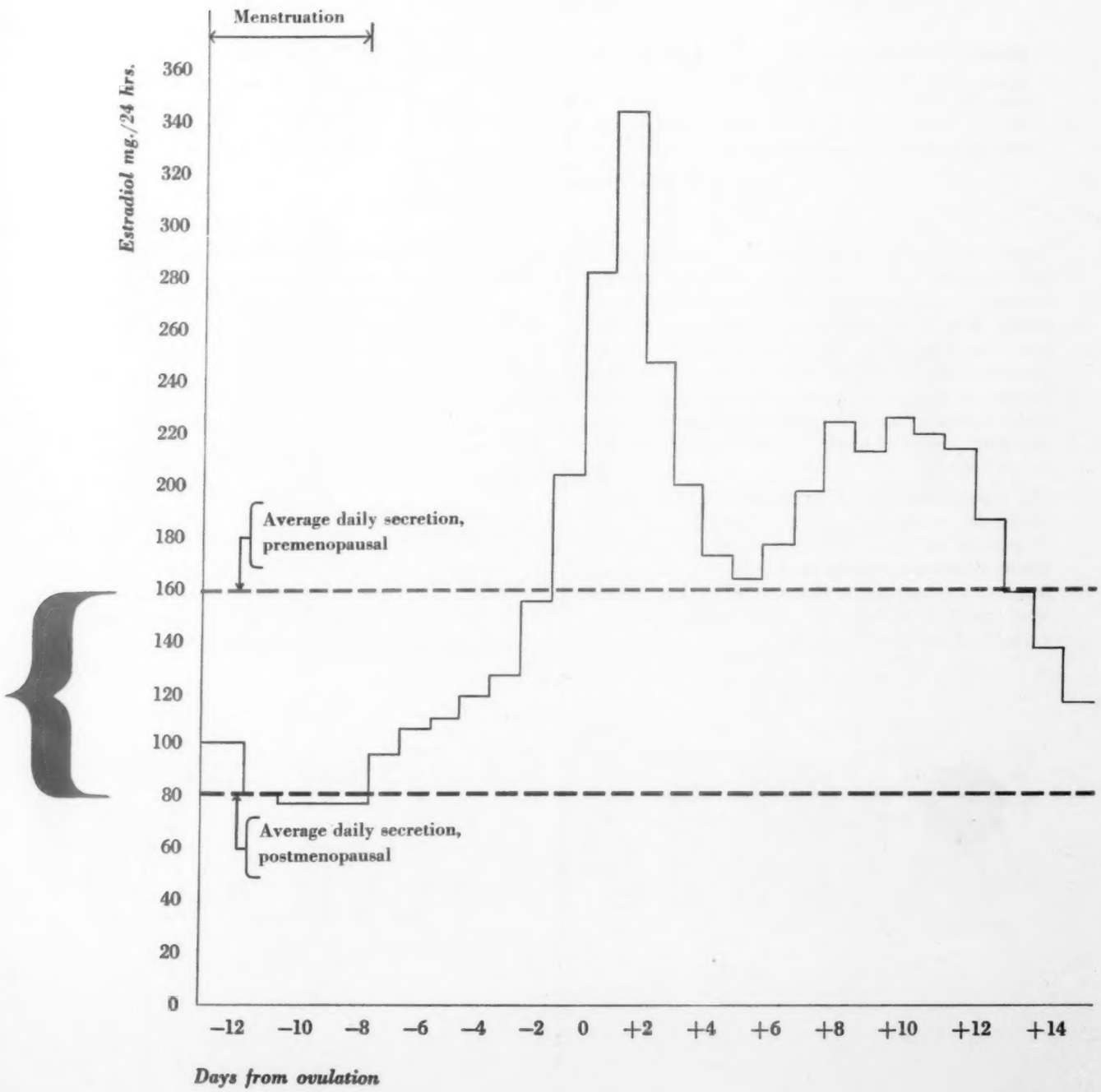
Each Halodrin tablet also contains 1 mg. of Upjohn-developed Halotestin* (fluoxymesterone)—the most potent oral androgen known. The primary purpose is to "buffer" the ethinyl estradiol just enough to prevent breakthrough bleeding, which is obviously undesirable in the menopause. It also exerts other beneficial hormonal effects, one of which, in common with ethinyl estradiol, is a powerful anabolic action so desirable in patients of advanced years.

Upjohn

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Endogenous estrogen secretion (mg./24 hours)
(calculated from average 24-hour urinary excretion of estradiol, estrone, and estriol)



IS THIS YOUR PATIENT?

1.



EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue

Posture is poor

No x-ray evidence of bone lesions

2.



LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain")

Patient is round shouldered, walks with a stoop

X-ray reveals compression fractures of lower vertebrae

3.



70 AND OVER

Fracture of hip after a minor fall

X-ray reveals fracture of neck of femur

X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of *low back pain, vague aches* and *fatigue* may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as *wrinkled and thinning skin,* a *tendency to appear older than stated years;* there may also be *hypercalciuria* when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteoblastic activity or retards the formation of protein and connective tissue such as *prolonged immobilization, cortisone therapy,* or *malnutrition* will favor development of osteoporosis in both male and female.

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"FORMATRIX" – each tablet contains:

Conjugated estrogens equine ("Premarin"®)	1.25 mg.
Methyltestosterone	10.0 mg.
Ascorbic acid	400.0 mg.

Dosage: 1 tablet a day – In the female, three weeks of treatment with a rest period of one week between courses is recommended.

Supplied: Tablets, bottles of 60 and 500.

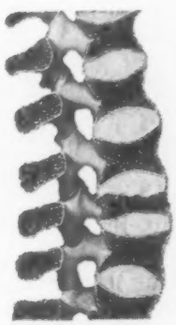
LITERATURE AVAILABLE ON REQUEST

1.



EARLY POSTMENOPAUSE
No x-ray evidence of bone lesion

2.



LATER POSTMENOPAUSE
X-ray reveals compression fracture of lower vertebrae

3.



70 AND OVER
X-ray reveals fracture of neck of femur

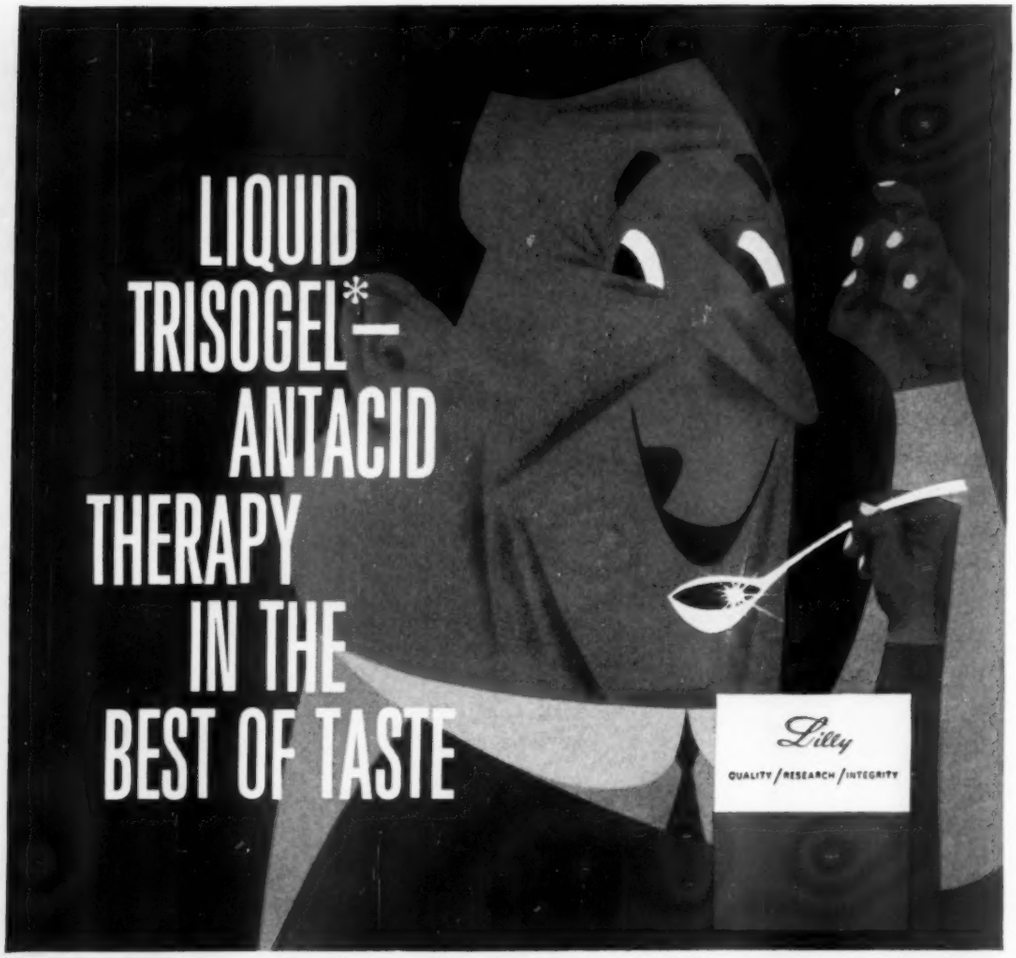
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in osteoporosis

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The American Journal of Medicine

VOL. XXV DECEMBER, 1958 NO. 6

Editorial

A Prospect of Richard Bright on the Centenary of His Death, December 16, 1958

"In all that relates to the clinical study of Bright's disease, the labors of Dr. Bright and of his followers have been attended by an amount of success unprecedented in the history of any other disease."
George Johnson, 1845 [*1*]

On the northwest wall of the bomb-torn St. James' Church in Piccadilly, London, there happily remains undamaged the memorial tablet dedicated to the memory of Dr. Richard Bright.* The inscription ends with these words:

"He contributed to medical science many discoveries and works of great value and died while in the full practice of his profession after a life of warm affection, unsullied purity and great usefulness."

Long before his death, Richard Bright had achieved immortality, and he has come down to us with a reputation that goes far beyond the eponymic fame by which he is recalled each day [*2*]. He died on December 16, 1858, of aortic stenosis, and was buried at Kensall Green. He was sixty-nine years old, the greatest clinician of his day, and one of the five or six great physicians of all time [*4*]. Born at Bristol of a family of bankers, he was educated at Edinburgh University and at Guy's Hospital where he was elected assistant physician in 1820, and it was there that he spent his professional life. A versatile, extraordinarily well balanced individual, he was in turn geologist, naturalist, linguist, traveller, popular author, clinician, clinical investigator and medical educator. Gifted with great powers of observation and analysis, his industry was prodigious, and his genius was blessed with a singularly accurate and lucid style of writing.

In 1827 there appeared Volume 1 of his renowned *Reports of Medical Cases, Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy* [*10*]. Volume 2 was published four years later [*11*]. It was in this book that he made known for all time the fact that in many patients with dropsy there are well marked lesions of the kidney and that in these cases the urine is coagulable by heat. The novelty of the discovery lay in the clinical, pathologic and chemical observations which he made and in the remarkably detailed researches undertaken by him and his colleagues. The importance of the discovery was the development of a new method for the study of disease in which correlations were made between clinical findings, morbid anatomy and histology, and biochemical observations.

Although Bright's fame rests on his recognition and description of glomerulonephritis, and on the introduction of analysis of the urine in the routine and day to day examination of patients in health and disease, it appears that his first love was neurology. The second of the two volumes of his wonderful book, crammed full

* As yet, no definitive life of Dr. Richard Bright has been published. Those who are interested in his life and times may wish to consult some writings about him. For convenience, I have included them in the references [*2–9*].

with new observations, was almost entirely devoted to descriptions of hemiplegia, epilepsy, cerebral tumors, meningitis and other diseases of the central nervous system. His principal observations make known to us the relationship of structure to function in the brain. Cases were produced to illustrate this thesis. He described many instances of what we now call Jacksonian epilepsy and, as Thayer [*7*] points out, he clearly recognized the significance of the syndrome. In all his writings on disease of the brain one can find many interesting and acute observations on cerebral localization based on the symptoms and signs he determined during life. He also made original observations on glycosuria, on steatorrhoea in pancreatic disease, on acute hepatic necrosis, cirrhosis, peritonitis, chorea, appendicitis, diaphragmatic hernia, heart block and whooping cough.

Bright's methods of clinical research called for close observation of the patient and his illness, at the bedside and in the clinic. He investigated the chemistry of their urine and blood during life and studied the morbid changes in the tissues after death grossly, by nephron dissection and with the microscope. He used this corpus of facts to test his hypotheses and to explain the phenomena and processes of disease.

To achieve his objects he developed a team of clinicians and chemists to help him; he organized the first clinical research unit in wards devoted entirely to clinical investigation; he collaborated with his colleagues outside Guy's Hospital to develop new technics to study the pathology of the kidney; and he used medical students to help him with his observations. He was also a talented teacher of medicine. Bright laid down principles for the training of doctors which we cannot afford to neglect today. He believed with Francis Weld Peabody [*12*] that "medicine is not a trade to be learned but a profession to be entered." He lectured to students, but he was essentially wedded to bedside teaching. In his writings on medical education [*13–15*] he stressed the need to work in the wards with the sick; the importance of continued observation of common clinical phenomena; the necessity for regular and repeated visits to those suffering from acute disease; and the fundamental importance of the study and interpretation of symptoms. He made innovations. He provided laboratories *in the wards* for students to work in and used clinical research to instruct his pupils. He seems to have had a keen eye for those with aptitude for research, and four of the "young friends and pupils" who, over the years, worked closely with him attained positions of eminence.*

Richard Bright did not have a hemoglobinometer, a sphygmomanometer, or cardiac catheters; but he had an insatiable inquisitiveness about the natural history, development and dynamics of progressive renal disease. We find him time and again seeking rational causes for clinical facts.

This desire to understand and explain the functions of the body in health and disease is evident throughout his writing, and it was this characteristic above all others, I believe, which impelled the medical staff in 1842 to set aside two wards at Guy's Hospital for clinical research [*16,17*].

Bright writes about his unit as follows: "The few following pages will be found to contain the record of the first experiment which, as far as I know, has yet been made in this country to turn the ample resources of an hospital to the investigation of a particular disease, by bringing the patients labouring under it into one ward, properly arranged for observation.

"Our establishment then consisted of a female ward with eighteen beds; a male ward with twenty-four beds; a room between the two wards for the meeting of the Physicians and Pupils, and for the registry of the cases; and a small laboratory communicating with the middle room, fitted up and decorated entirely to our purpose.

"The objects which we proposed to ourselves were, to examine, as far as it was possible, the changes which accompanied the secretion of albuminous urine in the various functions and secretions of the body; whilst at the same time we registered the various circumstances connected with the origin, progress, and treatment of the disease;—a disease than which there is certainly none which offers a more extended field for careful and well-directed observation."

The unit was also used for teaching students, and Barlow [*18*] notes that the wards were "expressly devoted to the purposes of bedside instruction and observation."

If one leafs through the transactions of the London Medical-Chirurgical Society, the Proceedings of the Royal Society and the Guy's Hospital Reports, from 1827 to 1858, it is apparent that an unnamed but vital "renal

* Doctors Barlow, Rees, Robinson and Toynbee.

association" existed in London in those years. Despite controversy the men concerned were closely tied together by affection for Bright whom they acknowledged as their leader and mentor.

The most important among these investigators was William Bowman [*19*], who studied the morbid anatomy of Bright's disease as well as the physiology and minute anatomy of the kidney; George Robinson [*20*], an experimental pathologist who first tied the renal veins of rabbits and thereby produced proteinuria; Joseph Toynbee [*21*], who developed nephron dissection in his microscopic studies of one hundred kidneys from Richard Bright's patients. Toynbee was the father of Arnold Toynbee, the eminent social philosopher and economist, and the grandfather of Arnold J. Toynbee, the historian. He became a famous otolaryngologist and raised his specialty from a quackery to a legitimate branch of surgery. J. Franz Simon [*22*], who first described the urinary sediment in detail, came from Germany to work with the pathologist George Johnson on the experimental production of Bright's disease in cats. Johnson [*1*] was the first to describe in detail the morbid anatomy of lipoid nephrosis, to discuss its pathogenesis, to draw attention to its diagnostic hallmarks—fatty casts and oval fat bodies—and "to distinguish microscopically in the urine the fatty from the acute or chronic inflammatory conditions of the kidney."

In 1845 Johnson [*1*] wrote, "that there is, perhaps, no single disease which has excited more interest among all classes of the profession than that form of renal degeneration, the existence of which was first made known by Dr. Bright and which has been named after that distinguished physician." This interest was also kindled in Europe where Bright's observations governing the interrelationships of edema, albuminuria and renal disease were readily accepted, and the contemporary literature was thoroughly reviewed in Pierre Rayer's three volume text "Traité des Maladies des Reins" [23], published in 1839, which was a milestone in the history of the subject. Rayer also described the passage of glanders from animal to man and he was the first clearly to recognize and describe lupus erythematosus.

Bright's team at Guy's Hospital consisted of "his young friends and pupils" Anderson, Barlow, Gorham, Reese and Tweedie, who made a number of surveys of the incidence of proteinuria in the hospital population. John Bostock [*24*], best remembered as the physician who first described hay-fever—being himself the patient—was Bright's chemist. With Rees, Babington and Barlow they correlated hypoproteinemia with proteinuria, and retention of urea with renal failure. Addison and Hodgkin, whose eponymic fame equals that of Bright, were friends and colleagues, and they were connected intimately with Bright's work.

Bright's influence on medical thought and teaching at Guy's Hospital made itself felt on successive generations in various ways. Partly through the luster of his name and partly through his relationship with Addison and Hodgkin, a famous line of physician-pathologists developed in the hospital during his active life and for the next sixty years. As John Ryle [*25*] points out, " . . . they carried on a tradition of faithful observation and record at the bedside, pursued and completed whenever possible in the postmortem room." Among these men were Golding Bird [*26*], who wrote a book on urinary diseases and was one of the first to make systematic analyses of urinary calculi; F. W. Pavy [*27*] and Walter Moxon [*28*] who described orthostatic albuminuria; and J. C. W. Lever [*29*], an obstetrician, who discovered that albuminuria was associated with puerperal convulsions and laid the foundations of our knowledge of eclampsia.

By 1870 Samuel Wilks [*30*] and Gull and Sutton [*31*] had recognized that certain cases of Bright's disease presented marked arterial changes which were found postmortem in patients with cardiac hypertrophy. As a result of careful anatomical and histologic researches they established for the first time that a disease of the arteries and capillaries existed in which early morbid change was attended with hypertrophy of the heart, but in which the kidneys were but little if at all affected. This was the first time essential hypertension had been recognized, but it was left to Dr. Frederick Akhbar Mahomed to give us the first detailed and complete clinical picture of essential hypertension—a disorder which he called "Bright's disease without albuminuria" [32]. This was a most important discovery but unfortunately Dr. Mahomed, who died at the age of thirty-five of typhoid fever, has not been given much credit for his observations, which preceded those of Volhard and Fahr, and Clifford Albutt, by many years.

Bright's last paper on renal disease was published in 1842 [*33*] and in it he tells of microscopical studies made with Dr. Joseph Toynbee which led them to believe that the most important changes in Bright's disease were to be found in the glomeruli. However, the distillate of his observations on the natural history of glomerulonephritis had been published in 1836 [*34*].

"The history of this disease," he writes, "and its symptoms, is nearly as follows:

"A child, or an adult, is affected with scarlatina, or some other acute disease; or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happen, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found, that already his urine contains a notable quantity of albumen: his pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of weight or pain across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy colour of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumen, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach, or the brain divide the care of the practitioner, sometimes drawing him away entirely from the more important seat of disease. The swelling increases and decreases; the mind grows cheerful, or is sad; the secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties: or he is perhaps, less fortunate;—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become oedematous, and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrence of his symptoms; or again, almost dismissing the recollection he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision indistinct; his hearing depraved: he is suddenly seized with a convulsive fit and becomes blind. He struggles through the attack; but again and again it returns; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed.

"Of the appearance presented after death, enough will be said in another part of the present communication: but one question may be asked in this place—Do we always find such lesion of the kidney as to bear us out in the belief, that the peculiar condition of the urine, to which I have already referred, shews that the disease, call it what we may, is connected necessarily and essentially with the derangement of that organ? After ten years' attentive—though, perhaps, I must not say completely impartial observation—I am ready to answer this question in the affirmative; and yet I confess that I have occasionally met with anomalies which have been somewhat difficult to explain."

In 1921 Hale-White [*4*] wrote feelingly about Bright's observations on renal disease [*10,33–37*]. "Assuredly," he stated, "this is one of the most

wonderful series of papers in medical literature. A disease which presents symptoms of derangement of almost every organ in the body is unerringly ascribed to the kidney. We are shown how to diagnose it. Its cause, its symptoms, its treatment and its postmortem appearances are given with such completeness and accuracy that after nearly a century no error has been detected in Bright's description."

To the clinician, the real impetus to new investigations is the patients he cares for. Those of us who are clinical investigators enjoy the study of patients at the bedside because it is from controlled observations of them that we begin to understand both physiology and pathology.

Richard Bright set standards of excellence in the controlled observations of patients which challenge all those engaged in the study of renal disease, and most of us honor him, as did Hale-White, for his discovery and description of renal disease. But I have tried to show that his real contribution was much more important even than this. What he achieved places him second only to William Harvey in British and perhaps in world medicine. William Harvey is renowned because he introduced the scientific method into the study of medicine, but Richard Bright taught us how to investigate disease at the bedside.

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Clinical Studies

A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families*

I. Streptococcal Disease Among Healthy Siblings

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GROUP A hemolytic streptococci most frequently invade the human body through the upper respiratory tract. Although primary streptococcal disease and its suppurative complications can now be effectively treated by penicillin, prevention of the occasional nonsuppurative complications such as rheumatic fever and glomerulonephritis remains a serious problem. Since prevention of these late nonsuppurative sequelae requires prompt recognition and adequate treatment of the antecedent bacterial episode, an appreciation of the varied clinical manifestations of beta hemolytic streptococcal disease becomes quite crucial.

Several surveys have documented the frequency of respiratory episodes in defined populations [*1–6*], and bacteriologic data from some of these studies [*2–6*] have delineated the prevalence and nature of streptococcal disease among affected persons. Thus, in a study of illness in a group of Cleveland families [*4,5*] 66 per cent of all observed illnesses were respiratory in origin, but less than 3 per cent of these respiratory infections were caused by beta hemolytic streptococci. Powers and Boisvert [*7*] have emphasized the importance of age in conditioning the manifestations of streptococcal disease in children, and reports from the armed forces concerning streptococcal respiratory disease in young adults indicate a clinical spectrum which ranges from acute exudative tonsillopharyngitis [*8–10*] to the asymptomatic carrier state [*11,12*].

Despite the valuable information provided by these reports on streptococcal disease, the methods of observation and selection of subjects tend to limit the usefulness of these findings in working out a practical approach to the prevention of rheumatic fever in school age children. In the case of data from the armed services, military discipline allows for excellent case finding, but the congested nature of a barracks setting is not comparable to civilian living conditions, nor does the age distribution of the young adult subjects coincide with the peak period of susceptibility to rheumatic fever. Data from children confined to orphanages or other institutions also are not representative of the general population. The study by Dingle et al. [*4*] comes closest to sampling a general childhood population, but here the socioeconomic level of the families seems far above that which is seen in most settings of rheumatic fever, and no data are presented concerning the streptococcal carrier state among these children.

The present paper is the first of two reports describing the results of three-year's experience with a program for the prevention of rheumatic fever and aims to supply comprehensive data concerning beta hemolytic streptococcal disease in a group of healthy school age children belonging to families that include at least one sibling

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with a definite history of rheumatic fever. This program was conceived as a long term study of the efficacy of penicillin prophylaxis of streptococcal infections in children recently recovered from acute rheumatic fever [*13–15*]. The importance of including observations on healthy children in prophylactic studies has been appreciated all too rarely [*16*]; data concerning the prevention of streptococcal disease in their rheumatic siblings is presented in the second paper [*17*].

MATERIAL AND METHODS

General Plan of Study. The study was originally designed to evaluate the efficacy of continuous penicillin prophylaxis in the prevention of streptococcal infection and recurrent rheumatic fever among children who had recovered from an initial attack of rheumatic fever. Healthy siblings of these rheumatic children served as controls to indicate the incidence of streptococcal infection in a particular household environment. These siblings, who did not receive continuous penicillin prophylaxis, constitute the clinical material of this report.

The data were collected during the thirty-four-month period from September 1953 through June 1956. The subjects were seen regularly at four-week intervals in a special clinic at the House of the Good Samaritan. The clinic routine was modified during the two summer months of July and August in 1954 and again in 1955 since it was believed that the prevalence of streptococcal disease was lowest during this summer vacation period, and it became apparent that family cooperation in clinic attendance would be enhanced if an annual respite of two months was allowed.

Selection of Families. Children between the ages of five and sixteen with a definite history of acute rheumatic fever were eligible for admission to this prevention program. The mother or guardian of each rheumatic child was encouraged to bring to the clinic at each visit at least one other healthy sibling who was closest in age to the rheumatic child. The "prevention" aspect of the program served to induce many parents to allow multiple siblings to attend the clinic as controls. However, during the first year of the study some families had no suitable siblings to serve as controls, and the rheumatic child alone was observed. After the first year, rheumatic children without suitable sibling controls were dropped from this study, and all new entrants to the study consisted of a rheumatic child receiving penicillin prophylaxis and at least one sibling not receiving prophylaxis. In families with multiple siblings, the one closest in age to the rheumatic child was considered the primary control, and all others were designated as secondary controls.

Clinic Visits. At each four-week interval the rheumatic child and his siblings were examined by a physician. Interval histories were recorded with emphasis placed on respiratory illnesses and manifestations of rheumatic fever. The rheumatic child was examined at each visit, particular attention being given to the auscultatory findings in the heart; each sibling control received the same examination. Laboratory studies at each visit included throat culture, erythrocyte sedimentation rate (Wintrobe), and antistreptolysin-O determination. These tests were made on the rheumatic child, sibling controls, and any other member of the family who attended the clinic because of symptoms. In addition to these clinic visits every four weeks, supplementary visits were encouraged at the time of respiratory and other illnesses. Physical examinations and appropriate laboratory tests were also performed at these nonroutine visits to the clinic.

Home Visiting Program. After the first six months it became apparent that acute febrile respiratory episodes often occurred between visits to the clinic and that children were occasionally too ill to be brought for examination. In order to provide more thorough bacteriologic documentation of these acute respiratory episodes before antimicrobial therapy could obscure their etiology, a home care program was instituted on March 1, 1954. After appropriate permission was secured from the family physician, the mothers were instructed to report by telephone respiratory symptoms occurring in any member of the family regardless of whether the particular subject was a regular participant in the study. Such telephone data were given directly to a physician, who decided whether the ill member of the family could safely come to the clinic or whether a home visit was required. All home visits were made by a physician who, in addition to his clinical examination, secured throat cultures from the sick member and from all other available members of the family. Follow-up home visits were made when indicated.

Laboratory Methods. Throat swabs obtained at a clinic visit were immediately streaked on Todd-Hewitt blood agar plates containing 5 per cent sheep red cells. The throat swabs obtained at home visits were similarly streaked within one hour after the home visit. Plates were incubated at 37.5°C., and colonies showing beta-hemolysis were subjected to subsequent grouping and typing by the capillary precipitin technic of Swift et al. [*18*]. Antibody titers against streptolysin-O were determined by a modification of the method of Hodge and Swift [*19,20*]. A rise in antistreptolysin-O titer was considered to be significant when there was at least a two-tube difference in dilution increments. When the rise was limited to two tubes, all the serums concerned were uniformly thawed from the sterile frozen state and retested against the same aliquot of streptolysin in order to confirm the rise. In addition electrocardio-

grams and chest roentgenograms were obtained, and cardiac fluoroscopy was performed, when indicated.

Definition and Classification of Streptococcal Illnesses. A diagnosis of "streptococcal infection" was made whenever either hemolytic streptococci were isolated by throat culture, regardless of clinical symptomatology, or a rise occurred in antistreptolysin-O titer by an increment of at least two tubes, even in the absence of a positive throat culture. All streptococcal infections were further subdivided into "symptomatic" and "asymptomatic" infections. The symptomatic group included moderate or severe cases of obvious exudative tonsillopharyngitis as well as milder cases of rhinitis and bronchitis, in which one might reasonably question the causal relationship between the streptococcus isolated from the throat and the mild symptomatology. The asymptomatic infections included instances in which there was laboratory evidence of streptococcal infection without clinical manifestations.

Multiple Streptococcal Infections. In a three-year study involving repeated observations of the same children, it became important to establish criteria for distinguishing the chronic carrier state from repeated infections in a single child. When a child demonstrated hemolytic streptococci on two separate occasions with a definite change in the specific type of group A organism, multiple infection was readily established. In cases of multiple isolation of streptococci in which the organism was of a specific type on one occasion and could not be typed on another, the distinction between the two streptococcal episodes became less clear. In such cases, an arbitrary interval of two months was selected; after this period it was assumed that the appearance in the throat of an organism that could not be typed signified a new infection.

Treatment of Streptococcal Infections. During the first fifteen months of the study (September 1953 through November 1954) all the rheumatic children were maintained on oral penicillin prophylaxis. Accordingly, when streptococcal infections were discovered among the healthy siblings of these rheumatic children the treatment of such infections consisted of a ten-day course of oral buffered potassium penicillin G.* Dosage was first established at 400,000 units daily taken in two tablets of 200,000 units each. When it became apparent that this dosage schedule was mainly suppressive but did not eradicate group A hemolytic streptococci, the therapeutic dose was increased to 400,000 units, three times daily, a total daily dosage of 1,200,000 units.

In December 1954, evaluation of benzathine penicillin G,† administered intramuscularly, in the chemoprophylaxis of rheumatic fever was introduced, and the families in the study were thereupon divided into two groups; in one the rheumatic child was maintained on oral penicillin administered daily, in the other the rheumatic child received one intramuscular injection of 1.2 million units of benzathine penicillin G at each four-week interval. With this change in the prophylactic program the siblings of the respective rheumatic children were treated differently at the time of streptococcal infections. For the remainder of the study the siblings were divided into an "oral group" in whom streptococcal infections continued to be treated with a ten-day course of oral buffered potassium penicillin G in the amount of 1.2 million units daily, and an "intramuscular group," in whom streptococcal infections were treated with a single intramuscular injection of 600,000 units of benzathine penicillin G.

In the great majority of patients with symptomatic infections a throat culture was obtained, and no treatment other than aspirin was given on the first day until results of the culture were available. If the culture proved positive for hemolytic streptococci, a second confirmatory throat culture was obtained, and penicillin therapy was immediately instituted. If the initial culture was negative, a second culture was also obtained, and treatment was withheld pending the results of this culture. The problem of transient positive cultures in asymptomatic subjects was encountered, but such patients were not treated with penicillin unless at least two of three consecutive throat cultures were positive for hemolytic streptococci.

Follow-up Laboratory Data. In order to evaluate the efficacy of both forms of penicillin therapy in the eradication of hemolytic streptococci from the pharyngeal flora, follow-up cultures were obtained at appropriate intervals after the start of treatment. In patients on the ten-day oral regimen of therapy three cultures were taken as follows: the first after eight to ten days of treatment, the second two to four days after therapy was completed, and the third eight to ten days after the completion of the course of treatment. After this the patient reverted to his usual routine of clinic visits with repeat cultures obtained at four-week intervals.

The management of follow-up throat cultures in the patients with streptococcal infections who were treated with a single injection of long-acting benzathine penicillin was comparable to that in the oral group. Since there was no equivalent termination of therapy, however, follow-up cultures were taken at eight to ten, twelve to fourteen, and eighteen to twenty days after the single intramuscular injection. By documenting each streptococcal infection and its post-treatment bacteriologic sequelae with these throat cultures, a more meaningful evaluation could be assigned to each form of penicillin treatment. Furthermore, the consistent collection of such data on post-treatment cultures in all patients with streptococcal infections and the typing of practically all group A organisms permitted more accurate distinc-

* Pentids® (E. R. Squibb & Sons, New York, New York).

† Bicillin® (Wyeth Laboratories, Inc., Philadelphia, Pennsylvania).

TABLE I

SUBJECTS AND OBSERVATION PERIOD: 1953–1956

Method of Prophylaxis for Rheumatic Siblings	Sibling Groups	No. of Children	Period of Observation (person-weeks)
Oral buffered penicillin G	Primary controls	85	4,678
	Secondary controls	67	3,367
	Total	152	8,045
Intramuscular benzathine penicillin G	Primary controls	47	2,184
	Secondary controls	36	1,610
	Total	83	3,794
	Grand total	235	11,839

tion between failure to eradicate bacteria completely and reinfection by a new strain.

The routine collection of serums at four-week intervals usually allowed for adequate evaluation of possible changes in antistreptolysin-O titer. However, where indicated, interim specimens were obtained between routine visits to the clinic.

Subjects and Observation Period. A total of 235 healthy siblings of rheumatic children were observed. As shown in Table I, these were divided into two groups depending upon the method of administration of penicillin prophylaxis to their rheumatic siblings. Since the long-acting intramuscular form of penicillin prophylaxis was not introduced until December 1954, the total number of healthy sibling controls for this group was smaller than in the oral group.

As the study progressed, new family groups were added, and other family units were dropped from observation for various reasons. All families without a suitable sibling to serve as a control were eliminated after the first year of the study, and institution of the home visit program required the further elimination of those families living in areas too remote for such home care. Also, families were dropped from the study when their attendance at regular clinic visits began to wane.

RESULTS AND COMMENTS

Role of Beta Hemolytic Streptococci in Common Respiratory Disease. During the period of this study a total of 603 symptomatic respiratory illnesses were recorded among the 235 children. The number of illnesses observed in any one child varied from one to twelve. The incidence of positive cultures for beta hemolytic streptococci in these illnesses is recorded in Table II.

These 603 illnesses were classified into six categories depending upon the most prominent symptomatic manifestation. (Table III.) Coryza with watery nasal discharge as the chief complaint was designated rhinitis, and such cases constituted the largest single group of illnesses. An illness with dominant sore throat of at least twelve hours' duration was arbitrarily classified as tonsillopharyngitis. Such cases constituted the second most frequent category of illness. A third major group of respiratory illness was bronchitis, in which cough was the major symptom. Three less common categories included episodes in which nausea, vomiting and abdominal pain predominated, instances of sudden acute fever of unknown origin (F.U.O.) without other respiratory symptoms, and a miscellaneous group that included such entities as sinusitis, pneumonia and the acute exanthemas.

Also shown in Table III is a relative frequency

TABLE II

INCIDENCE OF BETA HEMOLYTIC STREPTOCOCCI AND THEIR SEROLOGIC CLASSIFICATION IN 603 SYMPTOMATIC RESPIRATORY ILLNESSES AMONG 235 CHILDREN

Bacteriologic Classification	Total Illnesses	
	No.	%
No beta hemolytic streptococci cultured	519	86
Beta hemolytic streptococci cultured	84*	14

* Group A, 76. Non-group A, 8.

TABLE III

CLINICAL CLASSIFICATION AND BACTERIOLOGIC FINDINGS IN 603 SYMPTOMATIC RESPIRATORY ILLNESSES OCCURRING AMONG 235 CHILDREN OBSERVED DURING A THREE-YEAR PERIOD, 1953–1956

Clinical Classification	No.	%	Non-Streptococcal		Beta Hemolytic Streptococcal			
					Non-Group A		Group A	
			Total	%	Total	%	Total	%
Rhinitis	212	35.2	207	97.6	1	0.5	4	1.9
Tonsillopharyngitis	165	27.4	114	69.1	3	1.8	48	29.1
Bronchitis	149	24.7	140	94.0	2	1.3	7	4.7
Gastrointestinal	30	4.9	28	93.3	0	0.0	2	6.7
F.U.O.*	22	3.6	9	41.0	2	9.0	11	50.0
Miscellaneous	25	4.2	21	84.0	0	0.0	4	16.0
Total	603	100.0	519	86.1	8	1.3	76	12.6

* Fever of undetermined origin.

with which hemolytic streptococci were isolated from patients with these various illnesses. Thus, rhinitis, bronchitis and gastrointestinal illnesses were generally non-streptococcal in etiology. In such cases one might question whether the recovery of group A streptococci was etiologically related to symptoms or was rather a reflection of a coincidental carrier state during a non-streptococcal illness. In patients with tonsillopharyngitis, group A streptococci were isolated in approximately 30 per cent, consistent with the general concept that this bacterium commonly produces sore throat. Although there were only twenty-two patients who had sudden high fever without other respiratory symptoms (F.U.O.), in fully a half of these, illnesses were associated with positive cultures for group A streptococci.

Since fever in a sick child is probably the major determinant in a mother's decision about calling the family physician, the relationship of fever, as an index of severity of an illness, to the finding of group A hemolytic streptococci in the throat culture was analyzed. For this purpose an illness was considered "mild" if the patient's oral temperature did not exceed 100.6°F; the great majority of "mild" illnesses were actually associated with a temperature under 100.0°F. Illnesses were considered "moderate" to "severe" when the patient's oral temperature exceeded 100.6°F. An evaluation of the 603 respiratory illnesses (Table IV) revealed that positive cultures for group A hemolytic streptococci were obtained more than six times as frequently in patients with moderate to severe illnesses as in those with mild illnesses. These findings agree with the results of Keith and Carpenter [*10*] who recovered group A streptococci in 30 per cent of young adults with nasopharyngitis and temperature above 100.0°F.

The finding of beta hemolytic streptococci in 14 per cent of these 603 respiratory illnesses corresponds precisely with similar studies involving military personnel [*8,9*] and would suggest that the illnesses occurring among the younger age group of this study were equally prone to be associated with streptococci. Data on the incidence of streptococcal disease among children observed in Southern California [*21*] and the results of a streptococcal carrier survey in Minnesota [*22*] are also in close agreement, suggesting a minimal influence of climate on the bacteriological etiology of respiratory disease. The 90 per cent incidence of serologically

TABLE IV
BACTERIOLOGIC CLASSIFICATION OF 603 ILLNESSES ACCORDING TO SEVERITY OF CLINICAL MANIFESTATIONS

Bacteriologic Classification	Clinical Manifestations			
	Mild		Moderate to Severe	
	No.	%	No.	%
No group A hemolytic streptococci cultured (527)	414	95	113	68
Group A hemolytic streptococci cultured (76)	23	5	53	32
Total (603)	437	100	166	100

proved group A strains among the beta hemolytic streptococci isolated is also in keeping with military data for young adults [*9*] and in general confirms the results of other studies [*10,22,23*]. Such consistency of our data with the findings obtained in larger military surveys gives reasonable validity to subsequent analyses of the data obtained in this limited number of children.

The 29 per cent incidence of group A streptococcal cultures among 165 cases of tonsillopharyngitis observed in this study is at variance with the much higher incidence reported by others [*8,10,24,25*], but this difference may be attributed to the wider spectrum of cases included as "tonsillopharyngitis" in the present report. Most reports [*8,10,24,25*] limit the criteria of tonsillopharyngitis to the "follicular" or "exudative" variety, and the recovery of group A streptococci in such cases rises correspondingly to values between 50 and 80 per cent. Many of the cases classified as "tonsillopharyngitis" in the present study, however, were characterized chiefly by subjective sore throat without exudate and frequently without significant redness by inspection. A further variable that may alter the conclusions of seemingly comparable surveys of respiratory illness is the bacteriologic methodology; most workers have been alerted to such discrepancies in the isolation of streptococci [*21,26–31*]. In the present study the immediate plating of all throat swabs taken during clinic visits and the inoculation

TABLE V
BACTERIOLOGIC AND IMMUNOLOGIC EVIDENCE FOR 169 GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

Bacteriologic and Immunologic Evidence	Symptomatic	Asymptomatic	Combined Total	
			No.	%
Positive culture (with or without ASL-O* rise)	73	84	157	93
ASL-O rise (culture not taken)	1	1	2	1
ASL-O rise (antecedent cultures negative)	2	8	10	6
Total	76	93	169	100

* Antistreptolysin-O.

within one hour of cultures taken during home visits provided optimal conditions for streptococcal detection.

Identification of Group A Hemolytic Streptococcal Infection. Despite descriptions of classic symptoms and signs [*23,28,32*] the recognition of beta hemolytic streptococcal disease by clinical manifestations alone is quite difficult. In two separate studies that aimed to predict streptococcal disease on the basis of clinical evidence, bacteriological data confirmed the presence of hemolytic streptococci in approximately 70 to 75 per cent of the cases [*23,28*]. As clinical symptomatology becomes less overt, the accuracy of diagnosis becomes more and more dependent on laboratory methods.

In Table v the 169 group A hemolytic streptococcal infections observed in this study are listed according to the bacteriologic and immunologic data responsible for such classification. Although the twelve instances (7 per cent) of infection in which diagnosis was based on an antistreptolysin-O rise without positive cultures are included in our discussions concerning group A streptococcal disease, this must be considered somewhat arbitrary. Since *in vitro* studies by Todd [*33*] have demonstrated that streptolysin-O obtained from human strains of group C streptococci and from group G streptococci is serologically indistinguishable from that of group A, isolated rises in the titer of this antibody without associated positive cultures remains incomplete evidence for group A disease. Clinical studies [*6,9,27*] have demonstrated significant rises in antistreptolysin-O titers which were apparently related to infection with hemolytic streptococci of serologic groups C and G.

Clinical Characterization of Group A Hemolytic Streptococcal Disease. The clinical classification of the 169 group A hemolytic streptococcal infections has been documented in Table VI. The relatively large number of asymptomatic episodes (55 per cent) is higher than reported by others [*34*]. Packer et al. [*6*], observing forty-five children in the fixed environment of an orphanage, obtained weekly throat cultures throughout a year and found that one-third of those harboring group A streptococci were asymptomatic at the time of the positive culture. The greater incidence of asymptomatic infection in the present study may be related to the more variable and "open" environment of an outpatient population as well as to differences in

TABLE VI
CLINICAL CHARACTERIZATION OF 169 GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

	Total (no.)	Clinical Manifestations			Total (no.)
		Tonsillopharyngitis (no.)	Fever of Undetermined Origin (no.)	Miscellaneous (no.)	
Symptomatic	76 (45%)	.....	.....	.....	.....
Mild	.....	12	2	9	23 (30%)
Moderate to severe	.....	36	9	8	53 (70%)
Total	.....	48 (64%)	11 (14%)	17 (23%)	76 (100%)
Asymptomatic	93 (55%)	.....	.....	.....	.....
Total	169 (100%)	.....	.....	.....	.....

TABLE VII
ANALYSIS OF SEVENTEEN "MISCELLANEOUS" GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

Clinical Classification	Severity	Antistreptolysin-O Rise
Bronchitis	Mild	No
Bronchitis	Mild	Not done
Bronchitis	Mild	Yes, 6 tubes
Bronchitis	Mild	No
Bronchitis	Moderate	Not done
Bronchitis	Moderate	Not done
Bronchitis	Moderate	Yes, 2 tubes*
Rhinitis	Mild	Not done
Rhinitis	Mild	Not done
Rhinitis	Mild	Yes, 4 tubes
Rhinitis	Mild	No
Gastrointestinal	Moderate	No
Gastrointestinal	Moderate	No
Measles	Moderate	No
Varicella	Moderate	No
Otitis media	Mild	Yes, 4 tubes*
Infected finger	Moderate	No

* Isolated ASL-O rise without positive culture.

TABLE VIII
MAJOR CLINICAL FINDINGS IN SEVENTY-SIX SYMPTOMATIC GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

Clinical Manifestation	Severity of Manifestation		Total Patients Demonstrating Manifestation	
	Mild	Moderate	No.	%
Fever	15*	47†	62	82
Sore throat	33	17	50	66
Exudate	16	12	28	37

* Oral temperature between 99.6°F. and 100.6°F.
† Oral temperature over 100.6°F.

actual bacteriologic technics. The finding of this large segment of asymptomatic infection, however, indicates the difficulty of detecting and treating all group A infections on the basis of symptomatology alone.

In seventy-six symptomatic episodes of group A streptococcal disease only two-thirds were characterized by sufficient manifestations in the throat to warrant the classification of tonsillopharyngitis. Eleven episodes were accompanied by definite fever without other respiratory symptoms while seventeen illnesses fell into a miscellaneous group with symptoms not ordinarily considered streptococcal in origin. Thirty per cent of the total symptomatic episodes were mild, with the patient's oral temperature less than 100.6°F., while the remaining 70 per cent conformed to the more classic concept of streptococcal disease, with the patient's temperature above 100.6°F. and a clinical impression of moderate to severe illness.

The seventeen miscellaneous group A streptococcal infections are listed in more detail in Table VII. Of the twelve cases in which antistreptolysin-O data are suitable, the finding of an associated antibody rise in four is comparable to the results in the group with tonsillopharyngitis. The finding of group A streptococci in a patient with measles and in another with chicken pox illustrates the importance of throat cultures as the only precise means for finding streptococcal infection. Such random detection of streptococci in association with unrelated viral disease has obvious implications in the difficult task of eradicating streptococci and preventing such sequelae as rheumatic fever.

Since fever, sore throat and exudate are three of the common manifestations of symptomatic streptococcal illness, the seventy-six symptomatic infections were analyzed for the frequency of these findings. (Table VIII.) Fever would appear to be the most reliable clinical index of possible streptococcal disease, while sore throat, which was mild in most instances, is a less valuable guide in an empirical approach to the diagnosis of streptococcal respiratory disease in childhood. Exudate on the tonsils or posterior pharynx was observed relatively infrequently.

Serologic Types of Group A Streptococcal Infection. There were 157 infections from which group A streptococci were cultured, and all but six of these organisms were tested for serological type. (Table IX.) Twenty-one specific types were recovered from these infections, the most common being types 6, 3 and 25. In cases of type 25 organisms, the precipitin reaction tended to be quite weak.

In general, infections in several members of the same family tended to be caused by the same specific type of streptococcus. Whereas some workers [*35*] have suggested that the clinical features of streptococcal illness may be related in part to the serologic type, no such correlation could be detected in this study. Likewise, the observation that certain specific types of streptococci were more apt to produce a rise in anti-

TABLE IX
INCIDENCE OF SEROLOGIC TYPES OF GROUP A STREPTOCOCCI RECOVERED FROM 151* INFECTIONS

Serologic Type	No.	Serologic Type	No.
1	6	22	1
3	16 (11%)	25	10 (7%)
4	7	28	3
5	4	30	1
6	27 (18%)	32	1
11	1	39	1
12	3	42	1
13	3	43	1
14	6	44	1
18	1	46	2
19	2	Could not be typed	53 (35%)

* Group A organisms isolated from six infections were not typed.

streptolysin-O [*27*] was not borne out in this study.

The 35 per cent incidence of strains that could not be typed, which is comparable to that previously observed by us [*36*] but somewhat higher than that reported by others [*37,38*], may have several possible interpretations. From a study of the variations occurring in group A streptococci during the natural course of infection in man, Rothbard and Watson [*39*] isolated strains of bacteria during the first week of infection which were uniformly highly resistant to bacteriostasis and elaborated large amounts of type specific M substance. Conversely, strains isolated during convalescence showed greater susceptibility to bacteriostasis, loss of M substance, and could not be typed. A report [*8*] demonstrating a twofold greater increase in antistreptolysin-O titers following infections with strains of streptococci that could be typed as compared to strains that could not be typed has also served to emphasize the apparently greater invasiveness of streptococci that can be typed. Packer et al. [*6*], however, while agreeing that group A organisms that cannot be typed may be found more commonly in convalescent carriers [*40*], suggest that these strains may also indicate the lack of suitable typing serums rather than avirulent carrier strains. In their series eleven of twelve children with strains that could not be typed had an associated rise in antistreptolysin-O, and eight of these twelve children had respiratory symptoms at the time the organism was cultured.

In the present study strains of group A streptococci that could not be typed were recovered no more frequently from asymptomatic carriers (57 per cent) than strains that could be typed (52 per cent). There was no significant difference between the strains that could be typed and those that could not be typed in eliciting an antistreptolysin-O response in the host children. Since all persistent hemolytic streptococcal infections were promptly treated with penicillin, however, the relative infrequency of antibody rises may be related to the program of treatment rather than to the biologic properties of the streptococci.

Antibody Response during Hemolytic Streptococcal Infection. The study of a large number of streptococcal infections among these healthy siblings made it possible to collect data concerning the frequency with which an increase in antistreptolysin-O was stimulated by these infections. Several investigators [*41–44*] have stressed the importance of the antistreptolysin-O response during streptococcal disease and have pointed out that this antibody rise on the average is more frequent and quantitatively greater in those persons in whom late non-suppurative complications develop, such as rheumatic fever or glomerulonephritis. Although most reports [*11,24,25,43,45–48*] have shown that a rise in antistreptolysin-O occurs in between 80 and 90 per cent of patients with untreated streptococcal disease, in a few studies this percentage has been considerably lower [*30*]. Before examining the antistreptolysin-O data in the present study, however, it seems important to stress the possible interpretations of a streptococcal antibody rise and to list some of the variables that may affect this response.

At one extreme is the hypothesis [*27*] that a positive throat culture without an associated rise in antistreptolysin-O may mean that the streptococcus is not truly etiological but only coincidentally present in the throat. Possible differences in the ability of certain specific serologic types of group A streptococci to stimulate antibodies have been mentioned previously, and Rantz et al. [*49*] introduced the possibility of individual differences in host capacity to react to the same antigenic stimulus. Rantz [*50*] also stressed the importance of the level of the initial antibody titer prior to infection, since the greatest increases occurred in those with initially low titers. If a response did occur when large amounts of antibody were present at the

onset of infection, its relative magnitude was less than that which occurred when the initial titer was low. Finally, the documented finding [*6,9,27*] of antistreptolysin-O rise in patients infected with hemolytic streptococci of serologic groups C and G and the apparent identity of the streptolysins released by groups A, C and G [*33*] combine to make it difficult to interpret the significance of changes in this antibody. On the other hand, in patients in whom rheumatic fever develops, an increase in antistreptolysin-O may be the only evidence of antecedent streptococcal infection [*14,15,44*].

With the introduction of penicillin for the treatment of hemolytic streptococcal disease it quickly became apparent that prompt eradication of the streptococci by penicillin resulted in a marked reduction in the frequency of antistreptolysin-O responses [*35,36,40,41,43,45,46,48*]. Brock and Siegel [*51*] observed a definite correlation between the promptness of institution of penicillin treatment of streptococcal infection and the suppression of antibody response; even when the initiation of therapy was delayed for five days, there appeared to be a reduction in the proportion of patients in whom a rise in antibody occurred. Likewise, by comparing intermittent and continuous penicillin treatment, Kilbourne and Loge [*52*] found a striking suppression in the frequency and degree of antibody formation with continuous penicillin treatment as opposed to intermittent treatment and concluded that this suppression was proportional to the duration of effective antibacterial action. In the current study penicillin therapy was instituted fairly promptly after bacteriologic confirmation in the majority of cases.

Of the 169 streptococcal infections observed in this study, in 129 instances suitable antibody data were available for analysis, and are presented in Table x. It is apparent that the proportion of patients showing a rise in antibody was approximately the same, whether the infections were symptomatic or not. In the symptomatic infections the circumstances under which penicillin therapy was given would seem optimal for inhibition of antibody response. Parents had been alerted to seek medical help promptly; the study physicians were keenly conscious of possible streptococcal disease; laboratory methods were always available; both penicillin itself and medical care were provided without cost. Despite these favorable conditions, however, a significant immune response developed in almost half of the children infected with streptococci and the type of clinical manifestation made little difference in the response. (Table xi.)

The comparable frequency of antistreptolysin-O responses among the asymptomatic "carriers" may well be the result of a combination of factors. Since symptoms did not prompt obtaining a throat culture in these "carrier" episodes, it might be expected that the group A organisms recovered had been present for sufficient time to produce antigenic stimulation. On the other hand organisms present in the throat without causing symptoms in the host might represent a form of host-parasite symbiosis which might not call forth an antibody response. Examination of the fifty-one instances of antistreptolysin-O rise (Table xii) revealed that in

TABLE X

FREQUENCY OF SIGNIFICANT ASL-O RESPONSE AMONG 129 SYMPTOMATIC AND ASYMPTOMATIC PATIENTS WITH COMPLETE IMMUNOLOGIC DATA

Data	Symptomatic		Asymptomatic		Combined	
	No.	%	No.	%	No.	%
Significant ASL-O rise	24	41	27	39	51	40
No significant ASL-O rise	35	59	43	61	78	60
Total	59	100	70	100	129	100

TABLE XI

FREQUENCY OF ASL-O RESPONSE IN RELATION TO CLINICAL CHARACTERISTICS AMONG FIFTY-NINE SYMPTOMATIC GROUP A STREPTOCOCCAL INFECTIONS WITH ADEQUATE ASL-O DATA

Clinical Characteristics	Total	Positive Culture No ASL-O Rise		Positive Culture and/or ASL-O Rise	
		No.	%	No.	%
Tonsillopharyngitis	38	22	58	16	42
F.U.O.	9	5	56	4	44
Miscellaneous	12	8	67	4	33
Total	59	35	..	24	..

TABLE XII

ANALYSIS OF FIFTY-ONE ASL-O RISES IN RELATION TO PRESENCE OR ABSENCE OF ASSOCIATED CULTURE POSITIVE FOR GROUP A STREPTOCOCCUS AND TO CLINICAL MANIFESTATIONS

	Symptomatic						Asymptomatic	Total
	Tonsillopharyngitis		F.U.O.		Miscellaneous			
	Mild	Moderate	Mild	Moderate	Mild	Moderate		
ASL-O rise, throat culture negative	0	0	0	0	1	1	8	10
ASL-O rise, throat culture not done	0	1	0	0	0	0	1	2
ASL-O rise, throat culture positive for Group A streptococcus	4	11	0	4	0	2	18	39
Total	4	12	0	4	1	3	27	51

ten instances an antibody rise occurred in the absence of positive throat culture, and eight of these rises occurred in asymptomatic subjects. This suggests that antigenic stimulation by streptococcal organisms does indeed occur in asymptomatic subjects.

The finding of antibody rises among healthy children without an associated positive throat culture was an uncommon but pertinent development of this study. Others [*27,30*] have maintained that antibodies are most likely to develop in association with strongly positive throat cultures. The relationship between the degree of positivity of the throat culture and the subsequent antibody response has been examined in Table XIII. Blood agar plates were quantitated arbitrarily according to the number of group A beta hemolytic colonies observed. There is a clear-cut relationship between the number of colonies and the frequency with which a significant increase in antistreptolysin-O was observed. This points up the difficulty of interpreting the meaning of an isolated antistreptolysin-O response without positive culture in asymptomatic children. On the other hand, the occasional development of rheumatic fever in persons showing an increase in antistreptolysin-O titer without accompanying bacteriologic evidence of streptococcal infection [*14,15,44*] indicates that this immunologic sign cannot be disregarded.

TABLE XIII

RELATIONSHIP BETWEEN DEGREE OF POSITIVITY OF THROAT CULTURE AND OCCURRENCE OF ASL-O RISE AMONG 127* HEMOLYTIC STREPTOCOCCAL INFECTIONS WITH COMPLETE IMMUNOLOGIC DATA

Strength of Culture	Total Infections with Culture Data		Infections with Complete Immunologic Data		
	No.	%	Total	Significant ASL-O Rise	
				No.	%
Grade 3	89	57	74	33	45
Grade 2	44	28	27	5	19
Grade 1	24	15	16	1	6
Total	157	100	127	39	..

* Throat culture data not available in two cases with ASL-O rise.

Treatment of Group A Hemolytic Streptococcal Infection with Penicillin. Despite reports [*53,54*] which describe the experimental *in vitro* production of penicillin resistance in group A hemolytic streptococci, no authenticated clinical example of such resistance has been documented, and penicillin remains the drug of choice in treating group A streptococcal infections. Certain workers [*35,55,56*] have tested broad-spectrum antibiotics, such as chlortetracycline and oxytetracycline, but have concluded that penicillin is more effective in eradicating group A streptococci, decreasing antistreptolysin-O formation,

and preventing rheumatic fever. It is only among persons with a history of penicillin sensitivity that the use of broad-spectrum antibodies in the treatment of group A streptococcal disease appears to have any rationale. With this exception, the only variables that remain to be considered are the particular form of penicillin to be used, the route of administration, and the duration over which such therapy should be maintained. The importance of the latter is emphasized by the careful demonstration of Eagle et al. [*57,58*] that the objective of penicillin therapy is to maintain an adequate bactericidal level in the blood and infected tissues for as long as possible.

Penicillin was first administered by repeated intramuscular injection of either the soluble aqueous salt or longer acting chemical combinations which yielded satisfactory blood levels for periods up to forty-eight hours. Various reports [*29,59–62*] documented the efficacy of penicillin administered intramuscularly in treating both clinical illnesses and carrier states of hemolytic streptococcal infection. Goerner, Massell and Jones [*60*] found that the carrier state usually could be eradicated by treatment for ten days, and others [*62*] confirmed that shorter courses of therapy were considerably less effective. The inconvenience of repeated intramuscular injections of penicillin, however, soon resulted in attempts to combine penicillin with appropriate buffers so that oral administration might be possible; several reports [*63–65*] demonstrated that equivalent plasma concentrations were attained if three to five times the parenteral dose was taken orally. Such oral penicillin therapy of streptococcal infection has been used successfully for the treatment of acute illnesses as well as carrier states [*36,40,66–71*]. However, the advantages of oral administration were partially offset by the failure of some patients to continue medication for a sufficiently long period to eradicate the streptococcal organisms completely [*72*].

The introduction of N,N′-dibenzylethylenediamine dipenicillin (benzathine penicillin G) [*73,74*] made available a repository form of penicillin which seemed ideally suited to the treatment of group A hemolytic streptococcal infection. Prolonged blood levels after a single intramuscular injection of this material were demonstrated to be sufficiently high to exceed the sensitivity of most strains of group A organisms [*75,76*], and clinical experience has confirmed the efficacy of benzathine penicillin G in the treatment of clinical streptococcal disease [*37,51,61,77*] and eradication of the carrier state [*22,67,78,79*].

In the present study the treatment of group A streptococcal infections was carried out with oral buffered penicillin G or with benzathine penicillin G given intramuscularly. (Table XIV.) Among 169 streptococcal infections, four symp-

TABLE XIV

TYPE OF THERAPY AND EFFICACY OF INITIAL COURSE OF TREATMENT: 169 GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

Form of Treatment	Symptomatic Infections			Asymptomatic Infections			All Infections		
	Total (no.)	Success (no.)	Failures (no.)	Total (no.)	Success (no.)	Failures (no.)	Total (no.)	Success (no.)	Failures (no.)
No treatment	4	4	.....	35	35	.....	39	39	.....
Oral buffered penicillin G 200,000 units, twice a day for 10 days	10	8	2 (20.0%)	10	6	4 (40.0%)	20	14	6 (30.0%)
Oral buffered penicillin G 400,000 units, 3 times a day for 10 days	38	36	2 (5.3%)	27	20	7 (25.9%)	65	56	9 (13.8%)
Intramuscular benzathine penicillin G 600,000 units.	24	21	3 (12.5%)	20	19	1 (5.0%)	44	40	4 (9.1%)
Total	76	69	7 (9.1%)	92	80	12 (13.0%)	168*	149	19 (11.3%)

* One asymptomatic infection was treated with oral penicillin V.

TABLE XV
RELATIONSHIP OF TYPE AND PROMPTNESS OF INITIAL PENICILLIN THERAPY TO INCIDENCE OF ASL-O RISE AMONG FORTY-SIX SYMPTOMATIC GROUP A STREPTOCOCCAL INFECTIONS

Type of Therapy	Day of Illness When Therapy Began	Antistreptolysin-O Data		
		Total	With Rise	Without Rise
Benzathine penicillin G 600,000 units, intramuscularly	1	12	6	6
	2	2	1	1
	3	2	1	1
	4	1	1	0
	6	2	1	1
Total	..	19	10	9
Buffered penicillin G 400,000 units, 3 times a day for 10 days	1	14	6	8
	2	5	0	5
	3	2	1	1
	4	2	0	2
	6	1	0	1
	7	3	0	3
Total	..	27	7	20

tomatic illnesses and thirty-five asymptomatic streptococcal episodes were not treated with either drug and are excluded from considerations of penicillin therapy. The reason for not administering treatment in the majority of the thirty-five asymptomatic cases was that confirmatory throat cultures were negative. In twelve of the thirty-nine episodes which were not treated, the sole criterion for group A streptococcal disease was the ultimate detection of a significant antistreptolysin-O rise without an antecedent positive throat culture.

During the early study period the daily dose of oral penicillin used for treatment was 400,000 units given in amounts of 200,000 units twice daily. This regimen was the same as the dosage schedule which the rheumatic children were receiving for prophylaxis, and yielded a total failure rate of 30 per cent. In all instances of failure in treatment with the 400,000 unit daily dosage, throat cultures became negative while the patient was receiving penicillin but quickly reverted to positive when treatment was stopped. The high rate of failure in treatment with the 400,000 unit oral regimen prompted revision of the schedule of treatment to 400,000 units taken three times daily. The combined incidence of failure in treatment at this higher dosage schedule for ten days was 13.8 per cent.

Evaluation of the results of oral treatment in this study does not take into account the factor of patient cooperation. Despite close rapport which existed between study personnel and participating families, mothers occasionally admitted that the oral medication was frequently omitted, particularly when children were free of symptoms. Such omissions of medication may explain the poorer performance of oral penicillin among the asymptomatic children. Attempts to measure this factor of patient cooperation have confirmed the fact that the efficacy of oral penicillin increases as penicillin is taken more faithfully over a prescribed interval of treatment [*77*]. The importance of the total daily dosage of penicillin and of the duration of treatment which is needed to eradicate the streptococcus has been studied by many workers [*35,40,68–71,80–82*], and the present report aims only at comparing two arbitrarily selected dosage schedules which were administered for ten days.

Treatment with a single intramuscular injection of 600,000 units of benzathine penicillin yielded a total failure rate of 9.1 per cent, which is somewhat higher than that reported by others [*37,61,77,78*] and may be explained by the more frequent follow-up cultures obtained in the present study. All failures in treatment observed in this study were characterized by bacteriologic relapse only; in no instance was bacteriologic relapse accompanied by respiratory symptoms.

Although complete eradication of streptococcal organisms from the throat is a major objective of all forms of penicillin therapy, the suppression of antibody formation may well have considerable importance for the prevention of rheumatic fever. Thus, in a previous study at the House of the Good Samaritan [*44*], 53 per cent of seventy-six streptococcal infections associated with a significant rise in antistreptolysin-O titer were followed by definite recurrences of rheumatic fever whereas only 6 per cent of 108 infections without associated increase in antistreptolysin-O titer were followed by rheumatic fever. Therefore, the antistreptolysin-O responses in infections treated with two different therapeutic regimens were compared. (Table xv.) No significant differences in this relatively small number of cases are apparent. In order to minimize the influence

of delayed treatment in this comparison, only symptomatic infections with satisfactory antistreptolysin-O data were appraised since the presence of such symptoms seemed to provide an appropriate indication as to time of onset of infection.

No allergic reactions were observed in any of the eighty-five patients treated with oral buffered penicillin G or in the forty-four treated with injections of benzathine penicillin G. The intramuscular injection of benzathine penicillin caused local discomfort in the majority of subjects. In many the discomfort was relatively slight, but several children who previously had been treated with the oral regimen stated that they would prefer oral therapy. A definite systemic reaction, manifested by fever and generalized malaise, was observed in only one patient. This child also had severe pain at the site of injection.

Non-suppurative Sequelae of Group A Streptococcal Disease. The attack rate of acute rheumatic fever following untreated streptococcal infection has been estimated at between 2 and 5 per cent [*32,83–86*], and a variety of explanations have been offered for the differences in the incidence of the disease reported by epidemiologic surveys. Variations in the criteria for diagnosis of acute rheumatic fever account for some of these differences while seasonal factors, bacterial types, and differences in host susceptibility may all exert an influence on the ultimate development of rheumatic fever. The experience of all workers, however, is that adequate penicillin treatment of the antecedent group A hemolytic streptococcal infection will usually prevent initial and recurrent attacks of rheumatic fever. In the present study the subjects were siblings of children who had already suffered an attack of acute rheumatic fever, and this positive family history would seem to constitute an unfavorable host factor in these children. Favoring these same subjects, however, were the conditions of the study which allowed prompt recognition and treatment of streptococcal disease. These two opposing influences may account for the actual incidence of non-suppurative sequelae observed in this study.

If the usual occurrence rate of rheumatic fever following untreated streptococcal infection had prevailed in this study, the 169 infections observed might have resulted in three to eight cases of acute rheumatic fever. Despite careful follow-up of practically all the patients with streptococcal infections no instance of classic rheumatic fever was actually observed. In three persons, however, clinical events occurring in relation to a streptococcal episode were of sufficient interest to warrant a more detailed report.

In one of these cases, a thirteen year-old boy was seen during a routine clinic visit and found to be asymptomatic with a negative throat culture. Four days later he was still asymptomatic, but a throat culture, taken in conjunction with a clinic visit of another sibling, revealed the presence of group A streptococci. A confirmatory culture one day later was again positive, and the patient returned in two days for treatment with benzathine penicillin G. As the patient undressed in order to receive the intramuscular injection, a rash typical of erythema marginatum was seen over the back and buttocks. A blood test performed at this time revealed a normal erythrocyte sedimentation rate. The patient was treated with penicillin and remained asymptomatic. The rash faded over the next three days and cardiac examination remained within normal limits. The antistreptolysin-O titer had been elevated prior to this episode and showed no further rise. Continued observation of this patient at monthly intervals for an additional year revealed no recurrence of erythema marginatum, and the cardiac examination remained within normal limits.

Two additional cases are noteworthy in that murmurs of mitral regurgitation developed in both patients during the period of study. One of these subjects was a fourteen year-old girl with a history of Sydenham's chorea four years previously. There was no evidence of heart disease when she entered the study in January 1954. She failed to attend the clinic in February and March 1954 despite having had a sore throat in February. When she was seen in April 1954 there was a definite murmur of mitral regurgitation and, although her throat culture was then negative, a rise in antistreptolysin-O titer had occurred. The history of Sydenham's chorea was not elicited until after appearance of the murmur and explains why this child was not receiving penicillin prophylaxis. The second case concerned a three and a half year old boy in whom mitral regurgitation also appeared to develop in association with an antibody rise although classic manifestations of acute rheumatic fever were lacking. Upon detection of these murmurs both of these siblings were given continuous penicillin prophylaxis.

TABLE XVI

INFLUENCE OF TONSILS ON INCIDENCE, MANIFESTATIONS AND ASL-O RESPONSE OF GROUP A STREPTOCOCCAL INFECTIONS

Dimension of Comparison	Total in Analysis	Tonsils		Ratio of Tonsils In:Tonsils Out
		In	Out	
Number of children observed	235	144	91	1.58:1
Period of observation (person-weeks)	11,839	7,184	4,655	1.54:1
Group A streptococcal infection (symptomatic and asymptomatic)	169	120	49	2.45:1
Group A streptococcal infections with moderate tonsillopharyngitis	35	28	7	4 :1
Group A streptococcal infections with moderate F.U.O.	9	5	4	1.25:1
Group A streptococcal infections with ASL-O rise	51	30	21	1.43:1
Group A streptococcal infections (asymptomatic)	93	64	29	2.21:1
Group A streptococcal infections (symptomatic)	76	56	20	2.8:1
Isolated ASL-O rise	10	2	8	0.25:1

The latter two cases illustrate how the murmurs of organic heart disease may develop insidiously in spite of careful clinical surveillance and thus serve to emphasize the insidious nature of acute rheumatic fever on occasion. Furthermore, the occurrence of two such cases of valvular heart disease during optimal conditions for finding streptococcal disease illustrates some of the problems concerning the prevention of rheumatic heart disease.

Effect of Tonsils on the Incidence, Manifestations and Immunologic Response of Group A Streptococcal Disease. Prolonged observations of the healthy sibling subjects afforded material from which to evaluate the possible effect of tonsils on streptococcal disease. In Table XVI these results are presented by ratio comparisons of the data concerning the children whose tonsils were intact and those whose tonsils had been surgically removed. A majority of the 235 children still had their tonsils, giving a ratio over those without tonsils of 1.58:1, and the period of observations for these two groups reflected a similar ratio of 1.54:1.

When all 169 group A streptococcal infections without regard for symptomatology were apportioned according to the presence or absence of tonsils, the ratio of infections in those with tonsils was significantly greater than in those without tonsils. The results suggest that the presence of tonsils in the children of this study may have served as a predisposing factor in the development of group A streptococcal disease. Reports from the military [*11*] during streptococcal outbreaks have also suggested that subjects with tonsils yielded greater numbers of streptococcal organisms and tended to remain chronic carriers whereas recruits without tonsils produced fewer streptococci and got rid of organisms sooner.

Since the development of an immunologic response by the streptococcus may well be an important determinant of rheumatic sequelae, the fifty-one instances of antistreptolysin-O rise were also apportioned according to this tonsillar factor. The antistreptolysin-O responses occurred at close to the expected ratio, 1.43:1. When such comparisons were made by other workers prior to the use of penicillin therapy [*27*], the conclusion was similarly reached that rises in antibody tended to occur equally among those with and those without tonsils. Of the ten instances of isolated rises in antibody without an associated positive culture the ratio is reversed; isolated immune responses occurred more frequently in the children without tonsils (0.25:1). Although these ten observations are too few to yield significant statistics, the possibility remains that the presence of tonsils favors the finding of positive cultures, while the absence of tonsils may result in silent immunologic stimulation.

Seasonal Incidence of Group A Streptococcal Disease. The three-year span of this study permitted measurement of the seasonal incidence of streptococcal disease. Figure 1 shows the seasonal variations for total group A disease and for "significant" group A disease. The significant category omits all asymptomatic episodes, which would not ordinarily be detected, and those symptomatic episodes in which weakly positive

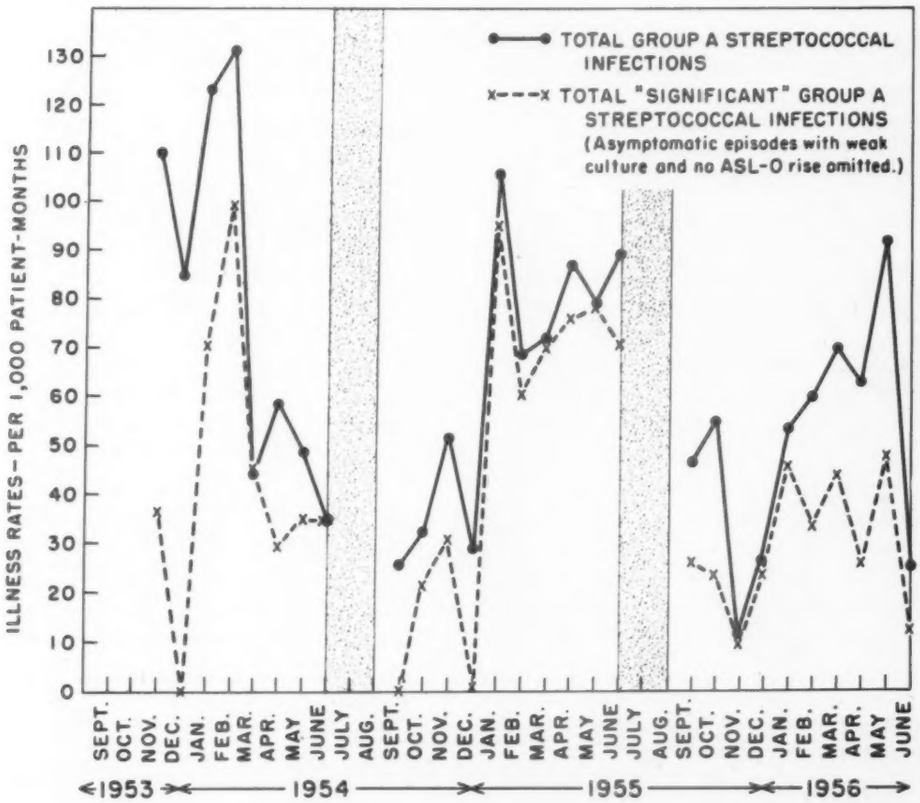


FIG. 1. Seasonal incidence of group A streptococcal infection: 1953–1956.

cultures without immune response suggest transient carrier states. The number of observations made in the months of July and August was insufficient to plot disease incidence. The three peak responses observed during the three-year period confirm the well documented maximum incidence of group A streptococcal disease in the late winter and spring months. Although these results show that streptococcal disease occurs primarily from January to June in northeastern United States, the organism is sufficiently prevalent the year round that a rational program of prophylaxis cannot be based on seasonal limitations.

Non-group A Hemolytic Streptococcal Disease. The ability of beta hemolytic streptococci to elaborate group-specific carbohydrates makes possible their serologic classification and assessment of their pathogenicity for various animal species. Group A strains constitute the major cause of hemolytic streptococcal disease in man although "human" group C strains and the large-colony types of group G are occasionally associated with human disease. During epidemiologic surveys of beta hemolytic streptococcal disease serologic identification of the strains of recovered organisms has revealed an incidence of non-group A strains which varies between 10 and 30 per cent [*6,8,9,22,40*]. Results of serologic grouping in the present study revealed forty-nine instances in which such non-group A streptococci were recovered from the throats of the sibling children. Of the hemolytic streptococci isolated from symptomatic illnesses 10 per cent were non-group A strains whereas 30 per cent of the asymptomatic episodes were associated with hemolytic streptococci of other groups. The over-all incidence of non-group A streptococci was 22 per cent, and details of these infections are given in Table XVII. Of the forty-nine episodes only eight were temporally related to overt clinical disease while forty-one isolations (84 per cent) were obtained from children who were well. The clinical symptoms in the eight cases corresponded to those in group A illnesses.

The significance of non-group A hemolytic streptococci must remain dubious since there is no apparent relationship between these strains and the subsequent development of non-sup-

TABLE XVII

CLINICAL CHARACTERISTIC, SEROLOGIC GROUPING AND ASL-O RESPONSE IN FORTY-NINE NON-GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS OCCURRING AMONG FORTY-FIVE PATIENTS

Clinical Nature	Total	Serologic Grouping					ASL-O Data		
		B	C	G	NG*	ng†	Rise	No Rise	Not Done
Symptomatic	..	..	..	..	..	..	.....	..	..
Tonsillopharyngitis (moderate)	..	..	..	..	X	..	X (5)‡	..	..
Tonsillopharyngitis (moderate)	..	..	..	..	..	X	.....	X	..
Tonsillopharyngitis (moderate)	..	..	X	..	..	..	.....	..	X
F.U.O. (moderate)	..	..	..	X	..	..	X (4)	..	..
F.U.O. (moderate)	..	X	..	..	..	..	.....	X	..
Bronchitis (mild)	..	..	..	..	X	..	.....	..	X
Bronchitis (mild)	..	..	..	X	..	..	.....	X	..
Rhinitis (moderate)	..	..	..	X	..	..	.....	X	..
Total (symptomatic)	8	1	1	3	2	1	2	4	2
Asymptomatic	41	9	10	12	10	0	5§	23	13
Total	49	10	11	15	12	1	7	27	15

* "Non-groupable" with available antiserums against groups A, B, C, D, G.

† No growth in sub-culture, although original colony was beta hemolytic.

‡ Figures in parentheses represent number of tubes.

§ These ASL-O rises associated with group C in three instances, group G in one instance and with a non-groupable organism in one case.

purative sequelae such as rheumatic fever. The importance of these organisms, therefore, seems to rest chiefly in their benign occurrence in the human throat and the possibilities of confusion with the more serious group A streptococci. Since groups A, C and G may elaborate antigenically similar streptolysin-O, the interpretation of increases in antistreptolysin-O in the absence of a positive culture may be difficult. Furthermore, the higher rate of failure in treating such non-group A infections with penicillin (Table XVIII) illustrates an important difference between these organisms and the uniformly high sensitivity to penicillin of the more widely prevalent group A strains.

TABLE XVIII

EFFICACY OF INITIAL PENICILLIN TREATMENT OF FORTY-NINE NON-GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS

Form of Therapy	Results		
	Total Infections	Total Failures	% Failures
None	15	..	...
Oral buffered penicillin G 200,000 units twice a day for 10 days	2	2	100
Oral buffered penicillin G 400,000 units 3 times a day for 10 days	21	12	57
Intramuscular benzathine penicillin G 600,000 units	11	2	18
Total	49	16	33

SUMMARY AND CONCLUSIONS

A program of penicillin prophylaxis in children recovered from acute rheumatic fever permitted observations on the incidence of hemolytic streptococcal infections among their healthy siblings. During the first three years of this program, data concerning respiratory infection were collected from 235 such healthy children who were observed over a period of 11,839 person-weeks. Throat cultures and antistreptolysin-O antibody levels served as the laboratory means of documenting all symptomatic streptococcal illnesses as well as asymptomatic streptococcal carrier states.

Of the 603 symptomatic respiratory illnesses recorded among these children, 14 per cent were associated with beta hemolytic streptococci, and 90 per cent of these organisms were found to be of the group A variety. The most frequent clinical category of respiratory disease encountered was coryza, but such mild symptoms of rhinitis were rarely accompanied by laboratory evidence of streptococcal infection. Tonsillopharyngitis was the second most frequent clinical entity and showed a correlation with group A streptococci of 30 per cent. Isolated fever was particularly associated with streptococci, and fever generally seemed to be the most important correlative finding of symptomatic streptococcal infection. Fully 55 per cent of all group A hemolytic streptococcal infections observed were asymptomatic carrier states detected in children who were presumably well.

The diagnosis of group A hemolytic disease was made by positive culture in 93 per cent of cases whereas immunologic response alone was the basis for diagnosis in 7 per cent. Many different serologic types of group A organism were detected among the 151 isolations which were typed. Type 6 was most frequently encountered among the strains which could be typed. Of the organisms studied 35 per cent could not be typed with the antiserums available.

Suitable data on antistreptolysin-O were available from 76 per cent of all group A hemolytic streptococcal infections observed and a significant antibody rise was detected in approximately 40 per cent of both symptomatic and asymptomatic groups of illnesses. The frequency of antibody response in the several categories of symptomatic streptococcal infection was about the same. Although the frequency of a significant antibody response seemed related to the numbers of streptococci in the throat, antibody rises occurred in the absence of positive throat culture in some cases. The 40 per cent incidence of antibody response occurred in spite of early diagnosis and fairly prompt penicillin treatment of most such bacteriologically documented infections.

Three regimens of penicillin treatment were studied. An oral ten-day regimen of buffered penicillin G in a daily dosage of 400,000 units was found to be suppressive for beta hemoloytic streptococci while the drug was administered, but bacteriologic relapse occurred in 30 per cent of patients so treated. A ten-day course of oral buffered penicillin G totalling 1.2 million units daily was highly effective in treating symptomatic infections, somewhat less effective in eradicating the carrier state, and gave an over-all incidence of failure of 13.8 per cent. A single intramuscular injection of 600,000 units of benzathine penicillin G gave a slightly lower over-all incidence of failure of 9.1 per cent. Although the oral program of treatment requires continued patient cooperation in actually taking the drug for a full ten days, this preparation was well tolerated with complete absence of side effects of allergic reactions. The long-acting intramuscular preparation was tolerated with freedom from allergic reactions, but patients did complain of transient pain at the site of injection and sometimes expressed a preference for oral treatment.

Although no overt indication of typical rheumatic fever was seen following these 169 streptococcal infections, two instances of rheumatic heart disease appeared insidiously, and one instance of erythema marginatum was detected.

The general occurrence rate of hemolytic streptococcal disease was greater among children of this study who still had their tonsils than among those whose tonsils had already been removed.

The three-year period of study confirmed the fact that hemolytic streptococcal disease has a year-round incidence with peak periods occurring in the late winter and early spring in this part of the country.

Finally data have been presented regarding the frequency and nature of hemolytic streptococcal infection associated with non-group A strains of this organism.

Acknowledgment: We are indebted to Drs. Sidney Brodie, Carrol Butler, Donald Fyler, Robert Goebel, Melvin Kaplan, Jacqueline Labesse, Florence Mayer, Theodore Mottu, Pauline O'Connell, Raymond Walther and Evangelia Zervopoulis for their assistance in the professional care of patients. The technical assistance of Miss Gloria Baker, Mrs. Helen Dockett, Miss Doris Foote, Mrs. Doris Hayes and Mr. Robert Perkins is gratefully acknowledged. Invaluable secretarial help was provided by Mrs. Elizabeth Sablone and Miss Sylvia Fleet. Penicillin used in this study was supplied by Dr. John T. Groel of the Squibb Institute for Medical Research. We thank Dr. Charles A. Janeway for his painstaking and thoughtful

criticism and corrections in the preparation of the final manuscript.

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A Controlled Study of Beta Hemolytic Streptococcal Infection in Rheumatic Families*

II. Penicillin Prophylaxis among Rheumatic Fever Subjects, Comparing Different Regimens

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THE close association of group A hemolytic streptococci with periods of rheumatic activity suggests that these organisms play a significant role in initiating the disease process in practically all cases. Evidence for this relationship is based on a combination of epidemiologic, bacteriologic and immunologic data which are now well documented [*1–12*]. In addition to this bacterial component in the pathogenesis of rheumatic fever, however, host factors also appear to be important, as only 2 to 5 per cent of untreated streptococcal infections are followed by acute rheumatic fever [*10,11,13–18*]. Since there are no known means of detecting beforehand which of a given group of children infected with streptococci will subsequently develop rheumatic fever, accurate diagnosis and prompt treatment of all streptococcal infections are crucial [*20*]. Of equal importance, however, is the prevention of streptococcal infections in persons who, having already experienced their first attack of rheumatic fever, are particularly liable to recurrence of the rheumatic process. According to statistics collected prior to the availability of effective antimicrobial drugs, such recurrences might be expected to follow streptococcal infections in from 20 to 80 per cent of cases [*8,10,12,15,19–27*].

Detection of clinically overt streptococcal disease is often difficult, but asymptomatic carrier states present further problems. Nearly half of all streptococcal disease is of the asymptomatic variety [*10,12,15*], and many rheumatic recurrences follow subclinical streptococcal episodes. Since the rheumatic fever episode itself may also be associated with minimal overt symptomatology [*7,28*] and yet produce progressive valvular deformity [*29*], continuous chemoprophylaxis against streptococcal infection among children recovered from acute rheumatic fever appears to be the most rational approach to the prevention of rheumatic heart disease.

Sulfanilamide and its several derivatives were the first drugs introduced for the prevention of streptococcal disease and rheumatic sequelae, and numerous reports [*21,24,26,27,30–42*] soon documented the efficacy of these compounds in reducing the recurrence rate of acute rheumatic fever. However, toxic reactions to the sulfonamide drugs were not infrequent among patients receiving these compounds, and the need for constant surveillance of such patients for possible leukopenia and nephropathic changes constituted a serious drawback in some cases. The ultimate development of sulfonamide resistance by certain group A streptococcal strains [*43,44*] and the subsequent availability of penicillin has now led to the wide use of penicillin in a variety of forms for the prophylaxis of streptococcal disease in susceptible persons [*20,39,40*].

Despite the continued use of penicillin prophylaxis no strain of group A streptococcus has developed resistance to penicillin *in vivo*, and the literature is replete with papers describing suc-

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cessful prevention of rheumatic fever by both prophylactic and therapeutic administration of a variety of penicillin compounds taken through the oral and parenteral routes [*23,45–49*]. Military installations also have utilized oral penicillin prophylaxis to suppress rising streptococcal carrier rates [*50,51*], and one report has described the partial success in the prevention of rheumatic fever among military recruits even when penicillin therapy for streptococcal disease was instituted too late to prevent an antibody rise [*52*].

Despite an abundance of clinical reports on penicillin prophylaxis, prevention studies comparing ambulatory rheumatic children with appropriate controls are surprisingly few [*53*]. The present study, the first three years of which are considered in this paper, was devised to assay the degree to which continuous penicillin would reduce streptococcal disease and recurrence of rheumatic fever among ambulatory rheumatic children as compared to their healthy siblings not receiving penicillin. One group of rheumatic children received oral penicillin prophylaxis for the full three-year period; another group of rheumatic children received long-acting repository parenteral penicillin at four-week intervals for the last nineteen months of this period. In addition, all patients hospitalized at the House of the Good Samaritan during these three years received daily oral penicillin in order to measure the incidence of streptococcal disease and recurrence rate of rheumatic fever among an inpatient rheumatic population. Progress reports of our experience have been published elsewhere [*54–56*]. This report presents controlled data concerning both oral buffered penicillin G* and long-acting intramuscular benzathine penicillin G† as prophylactic agents.

MATERIAL AND METHODS

Inpatient Study. Between September 10, 1953 and June 30, 1956, all patients admitted to the House of the Good Samaritan became subjects of the study during their period of hospitalization. The great majority of these patients were children of both sexes between the ages of five and sixteen years, but a small number of female patients over the age of sixteen were also included. With minor exceptions all subjects were persons with active rheumatic fever or a definite past history of rheumatic fever. A total of 452 such admissions were observed over 5,136 person-weeks.

Upon admission to the hospital each subject was placed in private room isolation for the first twenty-four hours pending results of throat cultures taken on admission. These throat cultures consisted of at least two separate swabs streaked separately on individual sheep blood agar plates. Blood was also drawn at admission for determination of the antistreptolysin-O titer. If the throat cultures taken on admission were negative for beta hemolytic streptococci, the patient was given oral buffered penicillin G in the amount of 200,000 units twice daily for the remainder of his hospital stay. If the throat cultures yielded beta hemolytic streptococci, a ten-day course of oral penicillin in therapeutic dosage was administered, and thereafter each such patient took the daily prophylactic amount of 400,000 units of oral buffered penicillin G.

Follow-up laboratory studies were directed to the recognition of group A streptococcal disease and consisted of repeat throat cultures and antistreptolysin-O determinations. For the first year of study throat cultures were taken somewhat more often than once weekly and over the entire study averaged at least once weekly. Whenever clinical symptoms or signs suggested possible streptococcal disease, the frequency and number of throat cultures were appropriately increased. Serial blood samples for antistreptolysin-O determinations were drawn at least once monthly.

All beta hemolytic streptococci isolated by culture were subjected to serological grouping and typing. A rise in antistreptolysin-O titer was considered an indication of streptococcal disease contracted within the hospital whenever such a rise followed two previous constant or falling titers. If an increase in titer occurred within the first month following admission to the hospital, such an antibody rise was considered compatible with infection contracted prior to hospital entry and therefore not indicative of failure of the prophylactic regimen.

Technics of culture, identification of hemolytic streptococci and antistreptolysin-O measurement were identical with those described in the previous communication [*57*].

Outpatient Study. The general organization of the outpatient study has been described in some detail in the previous communication [*57*]. A special clinic has been maintained at the House of the Good Samaritan since September 1953 in order to observe rheumatic children receiving penicillin prophylaxis and their healthy siblings not receiving penicillin. A classification of the various subject groups showing numbers and periods of observation is listed in Table I. The sibling controls have been subdivided into primary and secondary groups. A primary sibling refers to the child closest in age to the rheumatic subject, while the remaining brothers and sisters constitute the secondary siblings. Subsequent data for strepto-

* Pentids® (E. R. Squibb & Sons, New York, New York).

† Bicillin® (Wyeth Laboratories, Inc., Philadelphia, Pennsylvania).

TABLE I

PENICILLIN PROPHYLAXIS STUDY

September 1953–June 1956			December 1954–June 1956		
Oral Buffered Penicillin G (200,000 units twice a day)			Intramuscular Benzathine Penicillin G (1.2 million units every 4 wk.)		
Subjects	No. of Siblings	Observation Period (person-weeks)	Subjects	No. of Siblings	Observation Period (person-weeks)
Rheumatic children	114	6,545	Rheumatic children	47	2,498
Primary siblings	85	4,678	Primary siblings	47	2,184
Secondary siblings	67	3,367	Secondary siblings	36	1,610
Combined siblings	152	8,045	Combined siblings	83	3,794

TABLE II

GROUP A HEMOLYTIC STREPTOCOCCAL INFECTIONS AND RECURRENCES OF RHEUMATIC FEVER AMONG HOSPITALIZED PATIENTS RECEIVING ORAL PENICILLIN PROPHYLAXIS (HOUSE OF THE GOOD SAMARITAN, 1953–1956)

Year	Total No. of Patients	Period of Observation (person-weeks)	Total No. of Throat Cultures	Streptococcal Infections		Recurrences of Rheumatic Fever
				Positive Throat Culture	Antistreptolysin-O Rise	
1953–1954	184	1,799	2,895	0	0	0
1954–1955	160	1,982	1,675	1	0	0
1955–1956	108	1,355	1,502	1	0	0
Totals	452	5,136	6,072	2	0	0

coccal disease incidence have been calculated for each group of siblings as well as for the combined group.

Regular routines of clinic visits, the home-visiting program for interval illnesses, the collection of laboratory data and the classification of streptococcal illnesses have been described in the previous report [*57*]. Two-thirds of the children maintained on oral prophylaxis were followed for more than a year while one-fourth of the total were observed for the full three-year period. In the case of the intramuscular penicillin group, approximately two-thirds of the total number of forty-seven rheumatic children remained under observation beyond one year.

RESULTS

Inpatient Study. The incidence of group A hemolytic streptococcal infections and recurrences of rheumatic fever among the hospitalized patients receiving oral penicillin prophylaxis is shown in Table II. There were no recurrences of rheumatic fever among patients within the hospital during the entire observation period and only two cases in which group A streptococcal organisms were recovered from any of the 452 subjects.

Since the administration of daily oral prophylactic penicillin to the inpatient subjects was supervised by trained personnel, patient cooperation was presumably not a factor in the two "breakthroughs" of streptococcal infection. One of these occurred in an eight year old boy and the other in an eight year old girl. Both infections were detected by routine weekly throat cultures, and there were no associated clinical symptoms. The carrier state was promptly

TABLE III

HEMOLYTIC STREPTOCOCCAL INFECTIONS AND RECURRENCES OF RHEUMATIC FEVER AMONG HOSPITALIZED CHILDREN (HOUSE OF GOOD SAMARITAN, 1939–1945)*

No. of Patients	Period of Observation (person-weeks)	Hemolytic Streptococcal Infections	Recurrences of Rheumatic Fever	
			Definite	Suspected
1,097	20,852	135	58	41

* From: MASSELL, B. F., STURGIS, G. P. and MILLER, J. M. Factors influencing recurrences of rheumatic fever. Proceedings of the New England Cardiovascular Society, March 3, 1952.

eradicated by increasing the dosage of oral penicillin to 1.2 million units daily for ten days, and there was no subsequent rise in antistreptolysin-O titer in either case.

Some indication of the relative risk of streptococcal disease and the recurrence of rheumatic fever that might be expected in hospitalized patients not receiving penicillin prophylaxis is provided by the data of Table III taken from a previous study [*12*]. Grouping and typing of hemolytic streptococci were not routinely performed throughout this period.

Outpatient Study. Effect of penicillin prophylaxis on the incidence of group A streptococcal infections: In order to evaluate the efficacy of the oral dosage of prophylactic penicillin used in this study, the incidence of streptococcal infections among the rheumatic children and their siblings is compared in Table IV. In making this comparison, disease rates have been itemized separately for the primary siblings and the secondary siblings, but the combined sibling data have been used in evaluating the percentage of reduction in disease incidence achieved by the individual penicillin regimens.

The corresponding rates for total infections and disease among the rheumatic children receiving intramuscular penicillin prophylaxis and among their sibling controls are shown in Table V. The study period in total person-weeks of observation for these children was slightly less than half the observation period of the oral prophylaxis group. Since the incidence of symptomatic and asymptomatic infections was so similar in both groups of siblings, comparison of the relative efficacy of the oral and intramuscular forms of penicillin in suppressing streptococcal disease among the children receiving such prophylaxis seems justified.

If the streptococcal disease rates obtained for the healthy sibling controls are interpreted as representing the prevailing streptococcal exposure experience for these particular families during the observation period, the correspondingly lower disease rates among the rheumatic children may be assumed to reflect the protection afforded by penicillin prophylaxis. If the differences in rate of infection between the two groups of subjects are divided by the disease rates for

TABLE IV

RELATIVE INCIDENCE OF GROUP A STREPTOCOCCAL INFECTIONS AMONG RHEUMATIC CHILDREN RECEIVING ORAL PENICILLIN PROPHYLAXIS AND THEIR SIBLINGS NOT RECEIVING PROPHYLAXIS (SEPTEMBER 1, 1953–JUNE 30, 1956)

Subjects	No. of Subjects	Observation Period (person-weeks)	Symptomatic Infections		Asymptomatic Infections		Infections with ASL-O Rise		Total No. of Infections	
			Total	Rate per 1,000 (person-weeks)	Total	Rate per 1,000 (person-weeks)	Total	Rate per 1,000 (person weeks)	Total	Rate per 1,000 (person-weeks)
Rheumatic children.	114	6,545	7	1.1	19	2.9	14	2.1	26	4.0
Primary siblings.....	85	4,678	36	7.7	37	8.0	22	4.7	73	15.7
Secondary siblings...	67	3,367	16	4.8	27	8.0	10	2.9	43	12.8
Combined siblings...	152	8,045	52	6.5	64	8.0	32	4.0	116	14.5

TABLE V

RELATIVE INCIDENCE OF GROUP A STREPTOCOCCAL INFECTIONS AMONG RHEUMATIC CHILDREN RECEIVING LONG-ACTING INTRAMUSCULAR PENICILLIN PROPHYLAXIS AND THEIR SIBLINGS NOT RECEIVING PROPHYLAXIS (DECEMBER 1, 1954–JUNE 30, 1956)

Subjects	No. of Subjects	Observation Period (person-weeks)	Symptomatic Infections		Asymptomatic Infections		Infections with ASL-O Rise		Total No. of Infections	
			Total	Rate per 1,000 (person-weeks)	Total	Rate per 1,000 (person-weeks)	Total	Rate per 1,000 (person-weeks)	Total	Rate per 1,000 (person-weeks)
Rheumatic children..	47	2,498	1	0.4	3	1.2	1	0.4	4	1.6
Primary siblings.....	47	2,184	14	6.4	16	7.3	11	5.0	30	13.7
Secondary siblings...	36	1,610	10	6.2	13	8.1	8	5.0	23	14.3
Combined siblings...	83	3,794	24	6.3	29	7.6	19	5.0	53	13.9

TABLE VI

REDUCTION IN INCIDENCE OF GROUP A HEMOLOYTIC STREPTOCOCCAL INFECTIONS BY PROPHYLAXIS WITH ORAL AND INTRAMUSCULAR PENICILLIN

	Oral Penicillin			Intramuscular Penicillin		
	Infection Rate per 1,000 (person-weeks)		Reduction (%)	Infection Rate per 1,000 (person-weeks)		Reduction (%)
	Rheumatics	Combined Siblings		Rheumatics	Combined Siblings	
Total infections.....	4.0	14.5	72	1.6	13.9	89
Symptomatic infections.....	1.1	6.5	83	0.4	6.3	94
Asymptomatic infections.....	2.9	8.0	64	1.2	7.6	84
Infections with ASL-O*.....	2.1	4.0	48	0.4	5.0	92

* Antistreptolysin-O.

the sibling controls, an estimate of the percentage of reduction of infection achieved by penicillin prophylaxis may be obtained. Such estimated reductions in the incidence of streptococcal disease by both penicillin regimens have been listed in Table VI.

Further analysis of the streptococcal episodes occurring among the children receiving prophylaxis was directed toward delineating the nature of streptococcal "breakthrough" of prophylaxis. Of the four streptococcal episodes observed in children receiving intramuscular penicillin, two episodes occurred in the same child. The laboratory evidence for diagnosis in all four cases was a positive group A throat culture, and one of these episodes was also associated with a mild rise in antistreptolysin-O titer and the clinical symptom of sore throat. Three of the four positive cultures were obtained on the twenty-eighth day after the injection of penicillin. The fourth positive culture was obtained on the thirty-fourth day after penicillin injection and represented an instance of failure of the patient to report at the usual four-week interval.

The twenty-six episodes of streptococcal infection among the children taking oral penicillin occurred among twenty children, with two

"breakthroughs" in six children. The criterion of streptococcal infection in seventeen of these cases was a positive group A throat culture, and five of these seventeen infections occurred in association with clinical symptoms, especially fever. In nine of the total twenty-six streptococcal episodes designated as "breakthroughs," the sole evidence of streptococcal infection was a rise in antistreptolysin-O titer, antecedent cultures being negative. In addition, in five of the previously noted episodes with positive cultures there was a concomitant antibody rise, yielding a total of fourteen instances of antistreptolysin-O rise. A summary of the clinical and laboratory characteristics of the symptomatic group A infections occurring during penicillin prophylaxis is recorded in Table VII.

Prevention of rheumatic fever: Since the ultimate goal of continuous prophylaxis of streptococcal infection is the prevention of recurrences of rheumatic fever among susceptible persons, careful attention was directed to the detection of such recurrences. During the 6,545 person-weeks of observation of the rheumatic subjects given 200,000 units of oral buffered penicillin G twice daily, there were two definite recurrences of rheumatic fever. Among the forty-seven rheumatic subjects given 1.2 million units of benzathine penicillin G intramuscularly every four weeks and observed during a total of 2,498 person-weeks, there were no recurrences of rheumatic fever.

Details of the two recurrences of rheumatic fever reveal that one of these patients was known to be less than ideal from the standpoint of patient cooperation in taking the oral prophylaxis. This patient was a five year old boy who was discharged from the House of the Good Samaritan in August 1953 following recovery from an episode of Sydenham's chorea. Although he had been receiving continuous penicillin prophylaxis since his hospital discharge, he did not enter the study program until December 1953. At that time his antistreptolysin-O titer was 83 units and remained so through February 1954. At his clinic visit on March 3 he complained of slight sore throat and lassitude. Cervical adenopathy was noted at that visit, and laboratory data revealed an elevated sedimentation rate and a striking rise of antistreptolysin-O titer to 2,000 units although throat culture was negative. Two weeks following this clinical episode the patient was readmitted with recurrent chorea.

The second instance of rheumatic recurrence in the oral prophylaxis group occurred in a ten year old boy with a past history of rheumatic fever but no evidence of valvular heart disease. After a summer's absence from routine observation he was seen in early October 1955 and showed a single positive throat culture for group A streptococcus despite the absence of clinical symptoms and signs. Since confirmatory cultures were negative, no treatment was given beyond the continuation of the regular daily prophylactic dosage of penicillin. Routine clinic visits in late October, November and December revealed persistently negative throat cultures, no change in antibody level and no respiratory symptoms. In mid-January 1956, however, migratory arthritis occurred in conjunction with fever, tachycardia, an elevated sedimentation rate and the appearance of a murmur of aortic

TABLE VII

CLINICAL AND LABORATORY CHARACTERISTICS OF SYMPTOMATIC GROUP A STREPTOCOCCAL INFECTIONS OCCURRING DURING PENICILLIN PROPHYLAXIS

Form of Prophylaxis	Clinical Classification	Maximum Temperature (°F.)	Sore Throat	Exudate	Strength of Throat Culture	Antistreptolysin-O Rise (no. of tubes)
Oral	Tonsillopharyngitis	104.0	Mild	Moderate	Negative	5
Oral	Tonsillopharyngitis	102.0	Severe	0	Strong	0
Oral	Tonsillopharyngitis	103.0	Mild	0	Strong	0
Oral	F.U.O.*	102.0	Mild	0	Weak	3
Oral	F.U.O.	100.0	0	0	Weak	8
Oral	Bronchitis	98.6	0	0	Negative	2
Oral	Bronchitis	99.0	Mild	Mild	Strong	0
Intramuscular	Tonsillopharyngitis	98.6	Mild	Moderate	Strong	2

* Fever of unknown origin.

regurgitation. Throat cultures remained negative, and the antistreptolysin-O level did not rise.

Penicillin Tolerance and Reactions. Oral buffered penicillin G: The tolerance of the patients for oral buffered penicillin G was generally excellent. Among the 452 inpatients who received the continuous prophylactic amount of 200,000 units twice daily, there were only three instances when the drug had to be discontinued. In each of these three cases a pruritic rash developed that was attributed to the penicillin, and in all these cases there was a history of previous treatment with penicillin. In two instances the patient had been treated on a prior occasion with intramuscular benzathine penicillin G, and in one case the previous penicillin medication was penicillin V. There was no instance of nausea, vomiting or diarrhea attributable to oral buffered penicillin G.

One hundred fourteen rheumatic outpatient subjects were given 200,000 units of buffered penicillin G by mouth twice daily during 6,545 person-weeks. In not a single instance was any allergic or other untoward reaction encountered.

Intramuscular benzathine penicillin G: Experience with long-acting intramuscular benzathine penicillin G given in a dosage of 1.2 million units every four weeks was collected over 2,498 person-weeks. During this period forty-seven rheumatic children received a total of 644 intramuscular injections. All injections were given by physicians. It is to be noted that the subjects were not usually seen again for four weeks following injections, and information concerning reactions was generally obtained by history and not by direct examination.

Subjective reactions reported by these children were frequent. Of the forty-seven patients, forty-two complained of some degree of discomfort following at least one injection. In twenty-four cases the subject experienced only slight discomfort characterized by mild pain or tenderness at the injection site for one or two days following the injection. In eighteen instances the patients experienced more severe discomfort with moderate to severe degrees of incapacity in walking, which in a few cases required absence from school. Twenty subjects mentioned discomfort following the first two to four injections but little discomfort following subsequent injections. In four cases the severity of subjective reactions necessitated termination of this form of prophylaxis and reassignment of the patients to the oral program of prophylaxis. In addition to these varying subjective reactions in patients already receiving the long-acting injections, there were several instances of children who had already been receiving oral prophylaxis and who refused to be transferred to the intramuscular prophylaxis group because of fear of needles. On the other hand, some patients preferred having injections of benzathine penicillin to taking oral penicillin.

The objective evidence of intolerance for intramuscular repository penicillin was seen in the form of local reactions, constitutional reactions and allergic responses. Significant local reactions at the buttocks site of injection occurred in four patients. In one of these cases the mother reported a "black and blue large hard lump" which lasted one week, and another mother described "redness and swelling" associated with a lump that lasted three days. In both these cases injections were continued without recurrence of such local reaction. In another patient a sterile abscess developed following her sixteenth injection and a similar abscess was noted after her twenty-first injection, which finally necessitated discontinuation of intramuscular penicillin.

Constitutional reactions were limited to three episodes in which the mother reported low grade fever lasting one day following the injection.

Frank allergic reactions occurred in two rheumatic persons in the same family who had previously tolerated oral penicillin G. In the first child an urticarial rash developed twenty-six days after his first injection; it began to subside spontaneously but was severely exacerbated by a second injection of benzathine penicillin. In the rheumatic sibling of this patient a mild urticarial rash developed one week after her second injection. This rash persisted for twenty-three days. In both cases the regimen of intramuscular benzathine penicillin was discontinued, and both patients were again given oral buffered penicillin G without recurrence of hypersensitivity. An additional case of penicillin allergy developed one month after an injection of benzathine penicillin, but this child also showed rather complicated reaction patterns to the administration of penicillin in various forms. Although cessation of intramuscular prophylaxis with penicillin after the first injection in this child represents an instance of drug intolerance, the penicillin itself, and not the lc g-acting form, was the apparent sensitizing agent.

COMMENTS

Unlike the specific pathogenicity of a few serologic types of group A streptococci in producing nephritis [*18*], a wide variety of types may produce recurrences of rheumatic fever [*58*], and prevention of such recurrences is, therefore, dependent upon rigid control of all streptococcal episodes. Many drugs have proved to be effective in treating streptococcal infections [*59*] but the bactericidal action of penicillin appears to be superior in eradicating streptococci, decreasing antistreptolysin-O formation and preventing rheumatic fever. Estimation of the degree to which penicillin is effective as a prophylactic agent is dependent upon the use of suitable control subjects, and the present study has employed siblings of rheumatic children as the most ideal controls in comparing two forms of penicillin prophylaxis. Markowitz et al. [*60*] also compared the oral and intramuscular forms of penicillin prophylaxis, but their observations span only a single year and no control subjects were included.

Evaluation of oral penicillin in the prophylaxis of streptococcal infection and recurrences of rheumatic fever has been reported previously, but variations in the dosage of penicillin used and other conditions of study make comparison with this report difficult. Evans [*61*] gave a daily morning tablet of 100,000 units of penicillin to inpatient children convalescing from rheumatic fever and compared them with control children in the same convalescent home who received no penicillin. Over a two-year period of observation the control children showed a streptococcal carrier rate four times greater than that of the children receiving penicillin. In these controls, four recurrences of rheumatic fever developed, whereas the children taking penicillin showed no recurrences. Hofer [*62*] made a similar inpatient study, but the prophylactic dose of oral penicillin was increased to 100,000 units twice daily, with significant improvement in results. Sixty-three children receiving such prophylaxis over a seven-month period showed no symptomatic group A streptococcal disease, and only one carrier state developed, whereas in sixty-four control subjects convalescing from rheumatic fever there were four group A infections and eleven carrier states. In the present study the dosage of daily oral penicillin for inpatient rheumatic subjects was increased further to 200,000 units twice daily with even better results, since only two carrier states developed during a three-year observation period. The high degree of protection afforded by the conditions of the present study has several possible explanations. In addition to the increased total dosage of penicillin, which yields higher penicillin blood levels for more prolonged periods, the hospital setting obviates the need for patient cooperation in remembering to take his medication, and the nature of the hospital environment serves as a low reservoir for bacterial transmission.

Studies of the prophylaxis of rheumatic fever in outpatients have attempted to include control observations, but the control subjects have usually consisted of additional rheumatic children who were not given penicillin during the study period [*63–65*]. Exposure of children susceptible to rheumatic fever to further streptococcal infection is hazardous, and the differing household environments of the study subjects receiving penicillin and the controls introduces an additional variable in comparing the incidence of disease. By using healthy siblings of the rheumatic children as the control subjects, the present study omits the dangers of exposing susceptible children unnecessarily and aims further to maintain a constant environment for both sets of subjects.

The results achieved by prophylaxis with oral penicillin in preventing streptococcal infection among the rheumatic children of the present study indicate this method of prophylaxis to be highly effective. The twenty-six episodes of streptococcal "breakthrough," however, warrant some explanation. An important cause of failure in ambulatory children receiving continued oral prophylaxis may be forgetfulness of a healthy child to take the tablets daily. Mohler et al. [*66*] have documented failures in patient cooperation relative to oral medication, and the experience of the present study suggested that some "breakthroughs" occurred in children known to be less than ideal in remembering to take their prophylactic drug. An additional factor to be considered is defective absorption. Although serum levels of penicillin somewhat below average were noted in one child in whom a "breakthrough" developed despite apparently good cooperation, it is not known whether defective absorption accounted for a significant portion of the prophylaxis failures observed.

The results obtained among the children receiving intramuscular benzathine penicillin indicate a higher degree of effectiveness in the

prevention of streptococcal disease and rheumatic recurrences for this preparation than oral penicillin, and these results are in essential agreement with the findings of others [*26,27,60,67–73*]. The three bacteriologic "breakthroughs" which were detected on the twenty-eighth day after the injection of 1.2 million units indicate that the blood level of penicillin may be relatively low at that time, and one study [*71*] has shown that there was no detectable penicillin in the serum at the end of four weeks in one-third of the patients receiving such injections. The streptococcal "breakthrough" observed on the thirty-fourth day after injection in our study illustrates a factor of patient cooperation inherent in this intramuscular regimen of prophylaxis. Whereas oral prophylaxis may be carried on quite independently by the patient, forgetfulness or delay in reporting for the intramuscular injection at the four-week interval introduces a possibility for failure of prophylaxis equivalent to omission of the oral drug.

With the availability of two effective forms of penicillin prophylaxis during the outpatient study period of this report, it was observed that the somewhat greater efficacy of intramuscular benzathine penicillin was partially counterbalanced by the increased incidence of reactions in these same children receiving injections. The complete absence of side reactions in the entire group of children receiving oral prophylaxis is in keeping with the low reaction rate to oral penicillin reported by others [*50,51*]. Reactions to all forms of parenteral penicillin are uniformly greater than with oral preparations [*74*], and reports concerning side effects of intramuscular benzathine penicillin vary with the dosage of the drug tested and the degree of care given to follow-up observations. Thus the dosage of 1.2 million units employed in this study is known to give a higher incidence of adverse reactions than a dosage of 600,000 units [*49,74,75*], while the close rapport maintained with patients during repeated visits made possible the reporting of minor side effects. The two children in whom urticaria developed following benzathine penicillin injections and who were yet able to tolerate oral penicillin both before and after these reactions would tend to support the suggestion that repository forms of antigens possess greater antigenicity [*74*]. An additional case report [*76*] of a prolonged reaction to intramuscular benzathine penicillin occurring in a child who had previously tolerated oral penicillin lends some further evidence to the occasional risk of such parenteral injections.

The present study, therefore, seems to indicate that there is a place for both daily oral penicillin and repository long-acting penicillin in the long-range prophylaxis of streptococcal disease and rheumatic fever. Among reliable patients, who understand the importance of continuous prophylaxis, the oral program is effective and almost completely free of side effects. For those patients who tend to be lax in the taking of oral prophylaxis, benzathine penicillin, given intramuscularly, offers a more reliable means of preventing streptococcal disease but is associated with greater risk of side reactions. The ultimate decision as to which method should be used in a particular case must be made by physician and patient after due evaluation of the individual circumstances. Regardless of which route of administration is chosen, however, this study demonstrates the significant amount of protection provided by penicillin prophylaxis to rheumatic children living in a normal family environment.

SUMMARY AND CONCLUSIONS

Observations have been presented concerning the effectiveness of penicillin in the prevention of group A hemolytic streptococcal infections among children convalescing or completely recovered from acute rheumatic fever. A total of 452 inpatients at the House of the Good Samaritan received 200,000 units of buffered penicillin G twice daily over a three-year period. Outpatient studies included 114 subjects who received 200,000 units of oral buffered penicillin G twice daily and forty-seven subjects who received 1.2 million units of benzathine penicillin G intramuscularly at four-week intervals. Healthy siblings of both outpatient groups of rheumatic subjects did not receive prophylactic penicillin and served as controls for measuring the incidence of streptococcal disease in these particular family environments.

No instances of recurrence of rheumatic fever developed among the entire group of inpatients, and in only two of these subjects did asymptomatic carrier states with group A streptococci develop. There was no case of elevation of antistreptolysin-O among the hospitalized patients.

The oral regimen of prophylaxis achieved a striking reduction in streptococcal infections among the ambulatory outpatient children receiving penicillin as compared to their healthy

siblings not so protected, and the intramuscular administration of long-acting penicillin showed even greater efficacy as a prophylactic agent.

Two recurrences of rheumatic fever developed among the children taking oral penicillin, whereas no recurrences were observed among the children receiving intramuscular prophylaxis. Among the 452 inpatients there were three instances of pruritic rash which required discontinuation of the oral penicillin preparation. None of the 114 outpatient subjects showed adverse effects attributed to oral penicillin. Reactions to long-acting intramuscular penicillin included several instances of subjective discomfort at the injection site, occasional local induration with sterile abscess formation, occasional low grade fever and two instances of allergic hypersensitivity.

The results of this study have demonstrated the superior prophylactic benefit of repository injectable penicillin, but the risk of reactions has been greater than that of oral penicillin. Oral penicillin is an effective agent in the prophylaxis of streptococcal disease but requires continued cooperation by the patient in taking the oral drug. Both regimens have appropriate usefulness in the prevention of recurrences of rheumatic fever.

Acknowledgments: We are indebted to Drs. Sidney Brodie, Carrol Butler, Donald Fyler, Robert Goebel, Melvin Kaplan, Jacqueline Labesse, Florence Mayer, Theodore Mottu, Pauline O'Connell, Raymond Walther and Evangelia Zervopoulis for their assistance in the professional care of patients. The technical assistance of Miss Gloria Baker, Mrs. Helen Dockett, Miss Doris Foote, Mrs. Doris Hayes and Mr. Robert Perkins is gratefully acknowledged. Invaluable secretarial help was provided by Mrs. Elizabeth Sablone and Miss Sylvia Fleet. Penicillin used in this study was kindly supplied by Dr. John T. Groel of the Squibb Institute for Medical Research. We thank Dr. Charles A. Janeway for his painstaking and thoughtful criticism and corrections in the preparation of the final manuscript.

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Mucocutaneous-Ocular Syndrome with Intestinal Involvement*

A Clinical and Pathological Study of Four Fatal Cases

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THE term "mucocutaneous-ocular syndrome" has been proposed [*29*] as a general collective name for a group of syndromes characterized by ulceration of the mouth and anogenital membranes, skin rashes and inflammation of the eyes. The condition usually runs a chronic but intermittent course and is accompanied in some cases by involvement of the joints, respiratory tract and central nervous system. The nomenclature is confusing. The patients with marked oral and genital ulceration and serious eye involvement, particularly hypopyon-iritis, are usually described as having Behcet's syndrome. Patients with predominant skin manifestations and systemic upset are usually described as having "severe erythema exudativum multiforme," "erythema multiforme with systemic involvement" or Stevens-Johnson syndrome. In the French literature the term "ectodermose érosive pluriorificielle" commonly appears. There is so much overlapping in the symptomatology of the different syndromes that a sharp clinical distinction is hardly possible.

Grouping on the basis of etiology also appears to be impossible at present. Behcet's finding of inclusion bodies in the exudate from the eye and oral ulcers has not been generally accepted. Most attempts at isolation of a virus from patients with Behcet's syndrome have not been successful. Alm and Öberg [*3*] gave rabbits an injection of cerebrospinal fluid taken from a patient and produced an encephalitis, but they could not transmit this or isolate a virus. Sezer [*33*], however, reported isolation of a virus in one case, and recently Evans et al. [*15*] found a virus in a fatal case, which was neutralized by the serum from another patient in the active ulcerative phase of the disease. There are scattered reports of the finding of a virus in Stevens-Johnson syndrome and ectodermosis erosiva pluriorificialis.

The pathoanatomical lesions in these syndromes are rather uncharacteristic. The information available has been gained for the most part from biopsy specimens of skin, oral mucosa and eyes removed from patients with Behcet's syndrome, and from a limited number of patients at autopsy. The skin changes do not differ from those of typical erythema multiforme exudativum and consist of quite atypical chronic inflammatory changes. A few authors stress the point that the lymphocytes show a distinct tendency to perivenous localization [*2,18*]. The histological findings in mucosal erosions are similar to those in the skin [*21,36*]. The main lesions found in enucleated eyes are keratoconjunctivitis, iridocyclitis or definite panophthalmitis, but specific lesions have not been observed.

A fatal outcome in the mucocutaneous-ocular syndrome is uncommon. We have found thirty-four reported cases. The results of complete or partial necropsy were stated in twenty instances. In most of the fatal cases the terminal symptoms and main autopsy findings have implicated the respiratory tract [*4,8,16,17, 25,29,34,36,39*]. Bronchopneumonia, pneumonitis and particularly primary atypical pneumonia have been reported. Sometimes, however, it is difficult to decide whether the pulmonary symptoms are merely unspecific complications due to the poor general condition of the patient or an intergral part of the basic disease. Broncho-

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scopic and postmortem observations of scattered ulcerative lesions in the larynx and tracheobronchial tree [*2,5,32*] might indicate a direct relationship.

In another group of fatal cases the main findings were confined to the central nervous system [*1,7,15,20,26,31,35*]. Meningoencephalitis with scattered perivascular round cell infiltration, disappearance of nerve cells or even minor hemorrhages and necroses were the main findings. In the case previously described by one of us [*31*] the lesions were confined to the brain stem.

A fatal outcome due to involvement of the gastrointestinal tract has been described by Saugmann Jensen [*30*]. Several other reports, however, contain statements implying more or less severe gastrointestinal involvement. Thus von Hebra [*22*], who originally described erythema exudativum multiforme, observed in one case "in the small bowels similar red circles as on the skin." Osler [*27*], who studied the visceral manifestations of the erythema group, also mentioned intestinal manifestations in cases of erythema multiforme. In a subsequent paper [*27d*], however, he classified these cases as Henoch's purpura. Phillips and Scott [*28*] mentioned in passing that two of their nine patients with Behcet's syndrome had previously had painful lesions in the region of the tonsils and in the oesophagus. In the fatal case of Stevens-Johnson syndrome described by Bruins Slot and Schornagel [*8*] a necrotizing oesophagitis and petechial mucosal haemorrhages of the large bowel were found. In another case, reported by Womach and Randall [*39*], "the oesophagus in its middle third contained three small ulcers, the largest measuring 1.5 cm., penetrating into the muscle layer." Interstitial oedema and infiltration with round cells were present. The case described by Alexander and Cope [*2*] concerned a sixty-eight year old man with a twenty-year history of diarrhoea. The autopsy revealed a severe ulcerative stomatitis, with shallow ulcers in the pharynx, oesophagus and gastric mucosa. Costello [*10*] described four further patients, two with haematemesis and two with melena; one died and the autopsy revealed "congestion more evident in the duodenum." In one of the two fatal cases reported by Short [*34*] autopsy revealed "a large ulcer . . . with yellow tinge—in the jejunum and there were many superficial ulcers in the ileum." Bechgaard [*5*] reported on a patient with Behcet's syndrome who had chronic recurring melena and abdominal pain. The terminal part of the ileum and the ascending colon were removed and a segmental ileitis was demonstrated. Concomitantly Jensen [*23*] reported another case in which the autopsy (described by Saugmann Jensen [*30*]) revealed congestion and oedematous mucosa with yellow spots in the terminal part of the ileum; the large bowel contained blood. Histologically the mucosa was atrophic with prominent lymph follicles, but without inflammatory reaction. Crawford and Luikart [*12*] described a case of severe erythema multiforme with intestinal involvement. A barium meal showed "an ulcerating process involving the proximal three-fourths of the large bowel" and "proctoscopy . . . permitted observation of a few isolated ulcerations of 0.5 to 1.0 cm. in diameter in the rectal mucosa." Dresner [*13*], reporting a case of Stevens-Johnson syndrome, mentioned that blood and melena "with traces of mucus and necrotic tissue were passed by rectum." Evans [*14*] recently described a case of Stevens-Johnson syndrome in a sixteen-year old boy who, in addition to the classic symptoms, had abdominal pains and diarrhoea, and passed fresh blood and mucus. Halonen and Klemola [*21*] stated that proctitis is present in all recurrent cases of erythema multiforme, in some attacks at least. In one of their patients difficulty in swallowing suggested oesophageal scars.

Saugmann Jensen reported two fatal cases of Behcet's syndrome. One was a twenty-nine year old man with a three-year history of colitis who died of bowel hemorrhage. Necropsy revealed extensive ulceration of the large bowel with unspecific inflammatory reaction, and a fatty liver. The other was a thirty-eight year old woman with acute colitis, aphthous stomatitis and fever. Necropsy showed severe ulceration of the large bowel and rectum. Saugmann Jensen was the first to consider the haemorrhagic colitis in these cases as a special and hitherto unknown manifestation of Behcet's syndrome. A similar clinical observation was made by Cottini and Randazzo [*11*] who used the term, "cutaneous-muco-intestinal syndrome."

These references suffice to prove that although intestinal involvement is rarely mentioned as a major complication of the mucocutaneous-ocular syndrome, it is by no means a rare occurrence in these diseases. We here give a detailed report of four fatal cases with complete autopsy findings. In three of these cases the

intestinal involvement was of serious character and was considered the cause of death.

CASE REPORTS

CASE I. L. G., a forty-four year old farmer's wife, was admitted to the hospital on May 23, 1956, with a diagnosis of colitis. Since the spring of 1955, she had had relapsing skin eruptions; from February 1956 on she had also had relapsing oral ulcers, flatulence and diarrhoea. Gradually the diarrhoea worsened, there was general deterioration, weight loss and fever.

Physical examination revealed an undernourished severely ill woman. On face and limbs there was a polymorphous exanthem, consisting partly of pea-sized infiltrates with or without a central bulla, partly of macules and maculovesicles. The exanthema was predominantly localized to the anogenital region with pea-sized, painful infiltrated ulcers on the labiae. On the tongue were two grain-sized aphthous sores. There was bilateral conjunctivitis, but no iritis or keratitis. Rectoscopy revealed a congested, granulated haemorrhagic mucous membrane with multiple erosions.

The initial white blood cell count was 10,200 per cu. mm. with 2 per cent eosinophils, 8 per cent neutrophilic band forms, 60 per cent neutrophilic segmented granulocytes, 26 per cent lymphocytes and 4 per cent monocytes. The hemoglobin was 8.1 gm. per cent; erythrocyte sedimentation rate, 24 mm./hour; thrombocytes were 677,600 per cu. mm.; prothrombin (Owren), 94 per cent. Serum electrophoresis showed total protein 6.2 gm. per cent, with a low albumin and elevated α_2 and γ-globulin fractions. The serum cholesterol was 194 mg. per cent, serum iron 78 μg. per cent. The urine was negative for albumin and sugar, no sediment. The stools contained pus, blood and mucus. Results of the bacteriological examination of blood, urine and spinal fluid were negative. Bacteriological examination of cutaneous ulcers and stools was noncontributory.

The course was progressive and relapsing, with intermittently hectic fever. New skin eruptions and sores in the mouth and anogenital area appeared, and the conjunctivitis worsened. Rectoscopy suggested a polypoid hyperplasia of the mucous membrane with extensive ulceration which led to a perirectal abscess and fistulas to perineum and vagina.

The patient was treated with antibiotics (penicillin, sulphadiazine, tetracycline) but there was no observable response. Steroid therapy had a distinct but transitory effect. The bleeding per rectum increased and endangered the patient's life. Therefore a coecostomy was performed, but the wound would not heal and eventually ruptured. A huge sore developed terminally. The patient died in cachexia on November 11, 1956.

At autopsy (0.479/56) the body was extremely emaciated (weight 26 kg., length 157 cm.). The artificial anus in the right iliac fossa was surrounded by a large necrotic ulceration and an extensive sacral decubitus ulcer was also present. Skin and eye lesions as already described. On gross examination all organs were markedly atrophic and small. The tracheobronchial mucosa displayed no ulceration. The lungs were small (230 and 185 gm.) but air-filled without fibrosis or infiltrations. The heart was small (200 gm.) without indication of myocardial, valvular or endocardial lesions. No aortic or coronary atheromatosis was noted. The pleura, pericardium and peritoneum were normal, with no exudates. The urogenital organs were essentially normal, apart from injection of the bladder mucosa. The kidneys weighed 290 gm. The pancreas and endocrine glands presented no visible lesions. The spleen weighed 90 gm., was of normal consistency. No abnormalities were found in the osseous system. The meninges, brain and spinal cord were macroscopically normal. No ulcers were found on the tongue, in the pharynx, oesophagus, stomach or small intestines, the contents of which were normal. The coecostomy was widely patent. The mucosa of the colon was partly covered by fibrin deposits, the removal of which revealed irregular mucosal ulcerations. In the ascending colon and notably in the rectum, areas with oedematous, almost polypous mucosa were present between the ulcerations.

Histological examination of the lungs, kidneys, spleen, thyreoid, adrenals and pituitary gland was within normal limits. Numerous sections from the nervous system were likewise noncontributory, notably without evidence of encephalitis. Examination of a thoracic and a lumbar spinal ganglion revealed an abundance of brown lipopigment in several ganglion cells which were otherwise normal, without atrophy or pericellular gliosis. No inflammation or fibrosis was evident in the calf muscle but there was a moderate general atrophy ascribable to inactivity. The overlying skin was slightly atrophic but without evidence of inflammation.

Sections from the colon showed a marked nonspecific chronic inflammatory infiltration with lymphocytes and a few eosinophils and plasma cells in the mucosa, penetrating through the submucosa and muscle layer, in some places even into the subserous fat. No granulomas were present. The margins of the ulcers revealed simple fibrinoid necrosis. Especially in the subserosal layer, the lymphocytic infiltrations were predominantly found around the venules and capillaries but not around the arterioles or larger vessels. (Figs. 1 and 2). The liver displayed a moderate fatty degeneration, mostly at the periphery of the lobules. In all the organs special attention was paid to the vessels, but no evidence of general vascular disease (periarteritis, microthromboses) was noted.

CASE II. A. O., a forty-seven year old female factory worker, was admitted to the hospital on June 26, 1957, with suspected sepsis. She had had salpingitis in 1938. Since 1956 she had had diarrhoea and tenesmus, since February 1957 transitory arthralgia

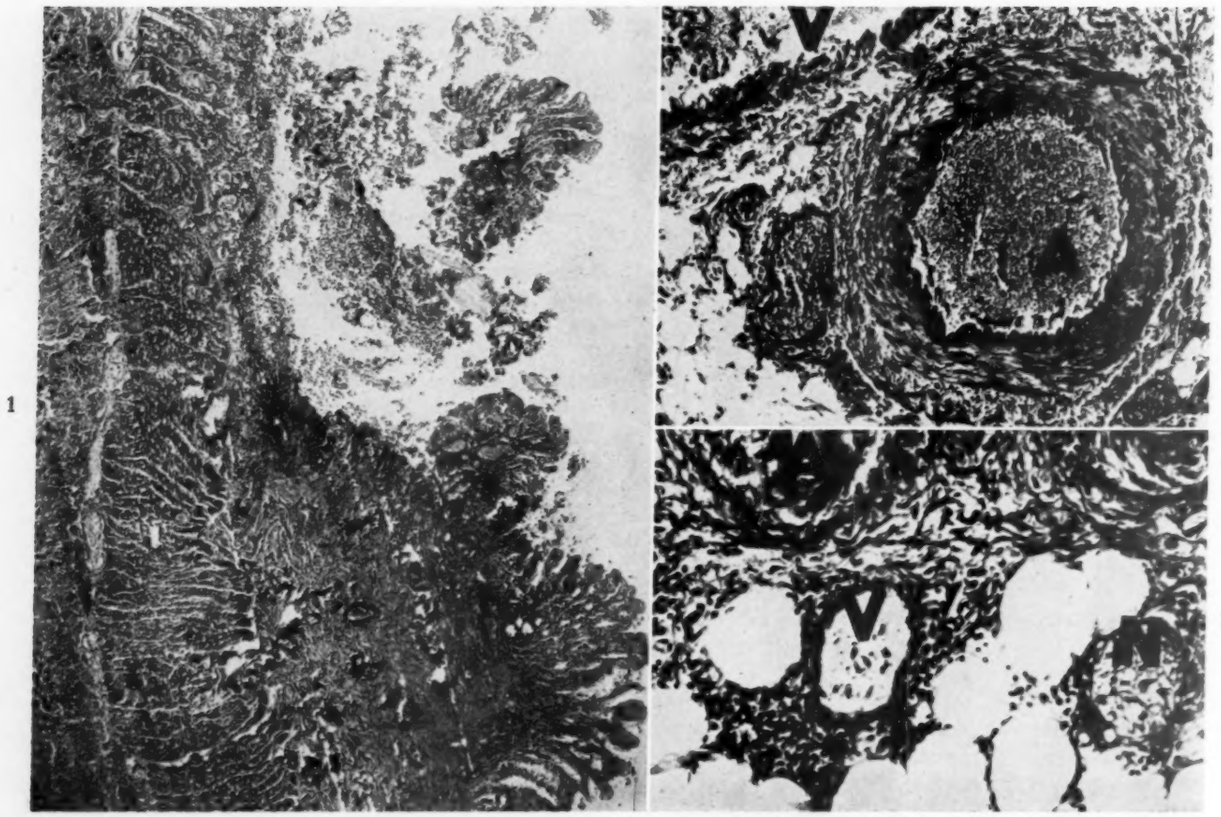


FIG. 1. Case I. Large bowel. Margin of large ulcer penetrating to the muscular layer. Note moderate nonspecific inflammatory reaction, in this case mainly limited to the margin of the ulcer. Hematoxylin and eosin stain.

FIG. 2. Case I. The subserous layer of the colon shows lymphocytic infiltration surrounding the capillary to the left, while the large arteriole (A) and the vein (V, upper left corner) appear normal. Hematoxylin and eosin stain, 10:1 planachromatic objective lens.

FIG. 3. Case II. Colon, showing the lymphocytes concentrated around a small venule (V) and to a lesser degree around a small nerve (N), while the arteriole transversely cut in upper border of picture (A) is unaffected. Hematoxylin and eosin stain, 10:1 planachromatic objective lens.

and fever. In June 1957 skin eruptions developed on the scalp and upper arms, with conjunctivitis, fever and painful anogenital ulcers.

Physical examination revealed a normally nourished woman in poor general condition. On both arms was found a symmetrical, polymorphous exanthem of the erythema multiforme type. Close to the anus was a pea-sized, infiltrated ulcer, and in the rima internates a 1.5 cm. long necrotic fissure. On the fauces and buccal membrane there were several superficial sores. A conjunctivitis was present in both eyes, but no iritis or keratitis. Over the left lung scattered high-pitched rhonchi were heard. Rectoscopic examination revealed a congested, easily bleeding mucous membrane with several small ulcers.

The initial white blood cell count was 6,600 per cu. mm. with 5 per cent eosinophils, 35 per cent neutrophil band forms, 43 per cent neutrophilic segmented granulocytes, 14 per cent lymphocytes and 3 per cent monocytes. The hemoglobin was 11.4 gm. per cent; erythrocyte sedimentation rate, 51 mm./hour; thrombocytes, 374,000 per cu. mm.; prothrombin (Owren), 66 per cent. Serum electrophoresis showed a total protein of 6.2 gm. per cent, with elevated α_2 and γ-globulin fractions. The thymol turbidity test was 1.8 units; alkaline phosphatase, 5.8 Bodansky units; total serum bilirubin, 1.4 mg. per cent. Repeated examinations for L.E. cells were negative. The urine was negative for albumin and sugar, the sediment contained a few pus cells. The stools contained pus, blood and mucus. Results of the bacteriological examination of the blood, urine and spinal fluid were negative. Bacteriological examination of the stools was noncontributory.

The course was progressive. The patient was initially severely ill with a hectic fever and explosive diarrhoea. Treatment with steroids and antibiotics (tetracycline, erythromycin) had an initially favourable effect on the general condition and on the conjunctivitis, enanthem and exanthem. The diarrhoea,

however, was uninfluenced and after two weeks of treatment the other signs relapsed. Abdominal pains and distention appeared, but there were no signs of peritonitis. Ultimately there were petechial haemorrhages on both legs and oedema of the left leg. The patient died on August 16, 1957.

Autopsy (0.395/57) disclosed a poorly nourished woman (weight, 51 kg.; length, 166 cm.) with oedema and cyanosis of the left leg. The skin efflorescences were only faintly visible. On gross examination the tracheobronchial tree contained mucopus but no ulcerations. No pleural effusion was noted but there were several petechiae on the pleura. The lungs (550 and 375 gm.) were congested and uniformly consolidated at the bases. No pulmonary embolism was noted. The pericardium contained 150 ml. serous fluid. The heart was small and flaccid (225 gm.) without valvular or endocardial lesions. The arteries were entirely free from atheromatosis. The kidneys (300 gm.) were pale, the pelves and ureters normal, but the bladder mucosa was strongly injected with ulcerations covered by fibrin. The internal genitals were normal apart from a walnut-sized subserous uterine fibromyoma. No vaginal ulcers were seen. The pancreas and endocrine glands were normal. The spleen was very soft (175 gm.). The osseous system and brain, with meninges, exhibited no visible lesions. A thrombotic mass occluded the left iliac and femoral veins.

Minor ulcerations were seen on the hard palate and large necrotic sores were present on the soft palate. The tongue, oesophagus, stomach and small intestines showed no ulceration. A very large extra- and retroperitoneal abscess extended laterally to the descending colon from the spleen to the bladder. There was no diffuse peritonitis, but a few fibrinous deposits and several adhesions were present in the left part of the abdominal cavity. The abscess originated from a 5 cm. necrotic perforation of the splenic flexure of the colon and contained yellow-green faeculent pus. The descending colon displayed extensive mucosal ulceration and inflammatory oedema, with loss of haustration, thickening of the wall and reduction of the lumen. Mucosal debris and fibrin were present as islands between the sores. Similar but less pronounced lesions were found in the rectum. A perineal ulceration surrounded the anus. The liver was small (625 gm.), yellow and soft; the biliary passages were unobstructed.

Histological examination of the myocardium, pancreas, brain (several sections) and spinal cord was noncontributory. The lungs displayed congestion, slight oedema and basal atelectasis, but no pneumonic infiltration. The kidneys were normal except for an isolated microthrombosis in a single arteriole. The necrotic ulcerations of the bladder extended into the muscle layer. A few polymorphonuclears were included in the fibrin covering the surface, but only a rather slight infiltration with lymphocytes and plasma cells was present beneath that. The spleen displayed hyperaemia and slight granulocytic infiltration in the pulp. The pectoralis major and biceps brachii muscles revealed a pronounced general atrophy and very slight interstitial connective tissue proliferation. The overlying subcutaneous fat was normal.

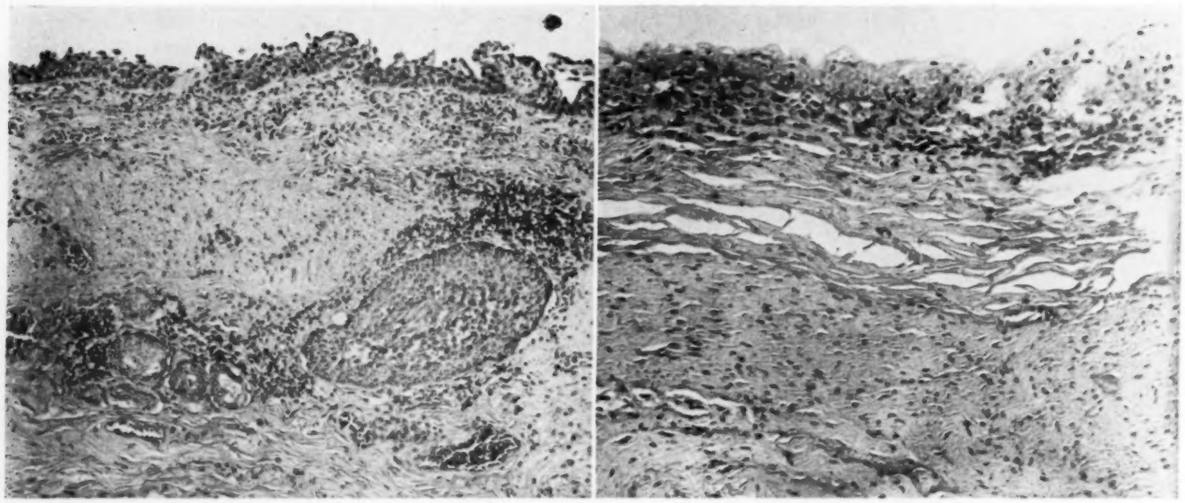
Sections from the descending colon and from the vicinity of the perforation in the splenic flexure displayed necrotic ulcerations extending deep into, in places even through, the muscle layer. Remnants of the mucosal membrane were seen like necrotic shadows. In spite of the profound ulceration the inflammatory reaction was surprisingly sparse, with only a moderate number of lymphocytes and plasma cells in the remaining muscle and subserous layers. The infiltrations were not particularly periarteriolar and the medium-sized vessels appeared normal. In places, however, the infiltrates were arranged around venules, capillaries and minor nerves. (Fig. 3.) Sections from the liver displayed a pronounced fatty degeneration but only inconspicuous cellular infiltration and no cirrhosis. No evidence of periarteritis or disseminated lupus erythematosus was found in the organs.

Case III.* H. H., a fifty-eight year old school-mistress, was admitted on July 7, 1957 to Bodø sykehus for iridocyclitis and Jacksonian fits. She had had three unexplained stillbirths. In 1952 she was operated upon for dacryocystitis; in 1956 for bilateral maxillary sinusitis. Since 1956 she had had increasing pulmonary symptoms and roentgenograms revealed peribronchial densities. Since March 1957 relapsing skin eruptions and oral ulcers had appeared. In May 1957 she had had several seizures in the right limbs. In June 1957 bilateral iridocyclitis recurred.

Physical examination revealed an undernourished, severely ill woman. On the scalp and limbs was found a polymorphous exanthem consisting of scattered efflorescences, from pea-sized papulopustules to serpiginous efflorescences several centimeters in diameter with infiltrated borders, some with central ulceration. There were several ulcers on the vulval mucous membrane, and an aphthous sore on the palate. Bilateral iridocyclitis was present. Over the lungs rhonchi and coarse crepitations were heard. Roentgenograms demonstrated widespread densities in both lungs and the maxillary sinuses. Neurological examination revealed motor dysphasia, hyperreflexia and a positive Babinski's sign on the right side.

The initial white blood cell count was 7,000 per cu. mm., with 6 per cent neutrophilic band forms, 48 per cent neutrophilic segmented granulocytes, 42 per cent lymphocytes and 4 per cent monocytes; hemoglobin, 10.6 gm. per cent; erythrocyte sedimentation rate, 50 mm./hour. The serum proteins were total 6.5 gm.; albumin/globulin ratio, 1:1. The thymol turbidity test was 3.1 units; alkaline phosphatase, 5.8 Bodansky units. Tests for L.E. cells were negative.

* A more detailed report of this case will be published elsewhere by Sulheim et al.



4 5

FIG. 4. Case III. Oesophagus. Note epithelial atrophy, fibrosis and infiltration with mononuclear cells in the mucosa and submucosa, and epithelial metaplasia in submucous glands. Hematoxylin and eosin stain.

FIG. 5. Case III. Small intestine (ileum). There is marked atrophy and moderate infiltration with mononuclears. The submucosa is atrophic and somewhat fibrotic. Hematoxylin and eosin stain.

Serological tests for syphilis were negative. The urine was negative for albumin and sugar, no sediment. The stools were not examined. Bacteriological examinations of the sputum and genital ulcers were noncontributory.

The course was progressive, the temperature rose and became hectic. New crops of skin rashes and enanthema occurred, and the eye and neurological complications worsened. Steroid therapy did not alter the course. Gastrointestinal signs were not observed. The patient died in cachexia on October 6, 1957.

At autopsy (P.6117/57) the body was emaciated. The exanthema were as described, visible on the breast and feet. Necrotic ulcerations were present on the left femur (biopsy specimen taken here) and on the right shoulder. A 2 cm. polycylic mucosal ulceration was noted in the hard palate, also an ulceration in the vulva. On gross examination the tracheobronchial tree showed no ulcerations. The lungs were small (both weighed 300 gm.), yellow-brown, with sparse air content and increased uneven consistency due to scattered and confluent areas of fibrosis. There were no cavernous lesions. The bronchial lymph nodes were essentially normal. The heart and vessels were essentially normal (the heart weighed 200 gm.). The serous membranes were normal. The urogenital organs showed no disease (kidneys weighed 300 gm.). The pancreas and endocrine glands were normal. The spleen was completely fibrosed and hypoplastic, weight 5 gm. No abnormalities were noted in the bones, brain, spinal cord, meninges. (The brain weighed 1,100 gm.). No gross lesions were noted in the gastrointestinal tract, the mesenteric lymph nodes were not increased in size. The liver (weighed 1,030 gm.) was normal, the biliary tracts were unobstructed.

Histological examination of sections from the myocardium, aorta, kidney, adrenals, ovary and muscle revealed normal structures. Sections from different lobes of the lung revealed a pronounced patchy interstitial fibrosis, in the main unconnected to the bronchial tree. The interstitial fibrous tissue was mostly poor in cells, but some areas contained several fibrocytes and fibroblasts. There were no findings suggestive of recent or old tuberculosis or other granulomas, there was no double refraction in polarized light or other findings indicative of silicosis, but abundant anthracotic pigment was noted. In places the fibrosis extended to the pleura, which was otherwise normal. A slight oedema and hyperaemia but no pneumonic infiltration was noted. The spleen was markedly fibrotic and contained only a few lymphocytes and no follicles. The vessels were thick and fibrosed, with a faintly metachromatic reaction to methyl violet. No "onion peels" suggestive of disseminated lupus erythematosus were seen. The bone marrow was slightly hypoplastic and contained a few plasma cells. Examination of the skin disclosed simple atrophy of the epidermis but no cellular infiltration of the corium. The gastrointestinal tract exhibited a general atrophy. In the oesophagus the epithelial covering was thin and less regular than usual. Some underlying mucosal glands revealed cellular metaplasia with squamous epithelium filling the lumina. A noticeable fibrosis and both periglandular and diffuse infiltration with lymphocytes was seen in the lamina propria and submucosa. (Fig. 4.) The gastric mucosa was markedly atrophic, with only few glands present and patchy

lymphocytic infiltration. Some sections from the fundus revealed a marked squamous metaplasia with only inconspicuous remnants of glandular structure. The underlying lamina propria contained coarse collagenous fibrils but only few cells. No gastric ulcers or localized scars were found. The ileum showed mucosal atrophy and desquamation, with both diffuse and focal infiltration with lymphocytes and a few plasma cells. The infiltration was mostly limited to the mucosa. Incipient ulceration was present in a few sections, but no deep ulcers penetrating into the submucosa were found. (Fig. 5.) Even the colon had a thin wall with mucosal atrophy and superficial inflammatory reaction but no ulcers were seen. Examination of the liver revealed slight chronic congestion but no fatty degeneration or cirrhosis. In sections from all the organs mentioned special attention was paid to the vessels, but no indication of vascular disease (disseminated lupus erythematosus, periarteritis) was found.

The brain was examined by Aa. Löken, M.D., neuropathologist, and revealed diffuse degenerative lesions with reactive gliosis and minor areas of demyelinization, notably in the cerebellum and brain stem but no conspicuous inflammatory reactions. The enucleated eye was examined by S. Ry Andersen, M.D., ophthalmopathologist, and revealed a subchronic panophthalmitis with bulbar atrophy and retinal gliosis.

CASE IV. A. W., a thirty-five year old teacher's wife, was admitted on February 2, 1955 after having been treated in a gynecological department for several years. Since 1940 she had had relapsing attacks of oral ulcers, skin eruptions and anogenital ulceration, and had been treated for relapsing conjunctivitis, episcleritis and notably iritis. Transient periods with slight arthralgia had occurred, accompanied in 1950 by erythema nodosum. From 1946 on anogenital involvement had dominated the picture, and since 1948 she had been admitted to the gynecological department eight times. In 1948 pea-sized vulval ulcerations and a couple of necrotic fissures in the rima internates were found. Rectoscopy disclosed normal findings. Due to the diagnosis of an anal fissure, anal dilatation was performed in 1947 but this was followed by faecal incontinence. A deep ulceration close to the anus was excised in 1949 but the wound ruptured and a rectal fistulation ensued. Several necrotic genital ulcers occurred and perforated into the rectum. Repeated perineoplasty was followed by complete wound rupture and the formation of a large, non-healing perineal sore. In 1950, preceding a new attempt at perineoplasty, sigmoidostomy was performed, with no better result. Rectoscopy now showed a proctitis, with a congested easily bleeding mucosa and several small ulcers distally. A last attempt at a perineoplastic repair in 1953 was again followed by rupture of the wound.

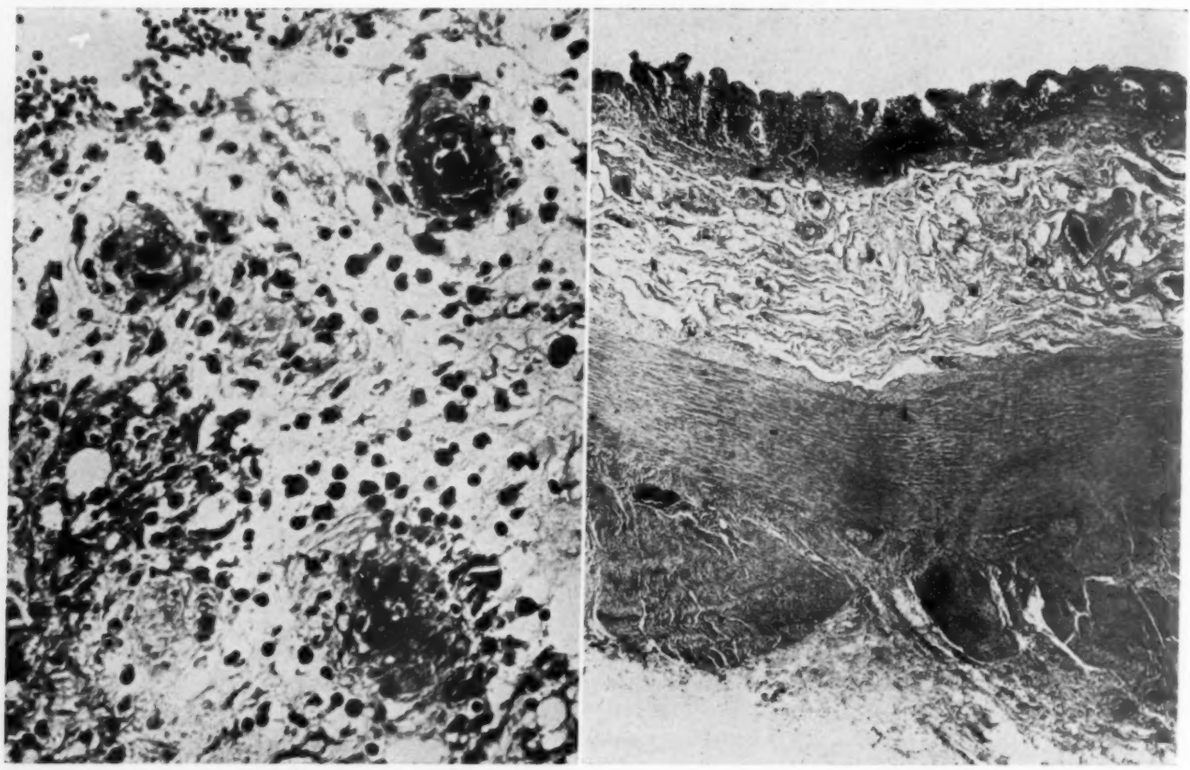
The general condition of the patient gradually deteriorated. Periods with a hectic fever intervened, accompanied by joint and eye involvement and exanthem. The stools from the artificial anus became foul and loose. Because systemic disease was suspected, the patient was transferred to our department.

Physical examination revealed an undernourished woman in poor general condition. There was no exanthema, except for two pea-sized papules on the buttocks. The anogenital region displayed several partly confluent necrotic ulcers, and there was a fissure in the rima internates. In the fauces were several small ulcers. An old iritis, but no active eye inflammation was found.

The initial white blood cell count was 11,200 per cu. mm. with 7 per cent neutrophilic band forms, 67 per cent neutrophilic segmented granulocytes, 25 per cent lymphocytes and 1 per cent monocytes. The hemoglobin was 11.4 gm. per cent; erythrocyte sedimentation rate, 77 mm./hour; prothrombin (Owren), 110 per cent. Serum electrophoresis showed a total protein of 5.7 gm. per cent, with low albumin and elevated α_2, β and γ-globulin fractions. The thymol turbidity test was 0.3 units; icterus index (Meulengracht), 3 units; serum iron, 20 μg. per cent. Tests for L.E. cells were negative. The urine was negative for albumin and sugar, no sediment. The stools contained pus, blood and mucus. Bacteriological examination of ulcers and the stools was noncontributory.

The course was progressive and relapsing, with periods of hectic fever, and recurrent iridocyclitis and episcleritis. The eye involvement could be controlled by local cortisone therapy. Systemic steroid therapy was followed by a transient beneficient effect on the general condition, but had no affect on the diarrhoea, which gradually worsened. Beneath the artificial anus a large abscess occurred and was incised. A second abscess perforated spontaneously, and stool was evacuated through these openings. The patient died in cachexia on November 16, 1955.

At autopsy (473/55) the body was extremely emaciated (length, 159 cm.; weight, 42 kg.) and displayed crural oedema. Lateral to the artificial anus in the left iliac fossa a spontaneous faecal fistula was present, the surrounding skin being undermined. Additional findings were a sacral ulcer and a large necrotic perineal ulcer extending into the vagina and rectum, the orifices of which were separated only by a thin bridge of skin. On gross examination the organs were markedly atrophic. The respiratory and circulatory organs were not diseased (lungs weighed 270 gm. and 180 gm., heart 180 gm.). The pleural and pericardial membranes were normal. The kidneys were small and pale (weight, 225 gm.). A very small uterus was present. The pancreas was normal. The thyreoid gland (weight, 10 gm.) and adrenals were atrophic. The spleen was flabby (weight, 125 gm.). The osseus system displayed osteoporosis. The brain and meninges appeared normal. The upper part of the



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FIG. 6. Case IV. Necrotizing vasculitis, from margin of chronic perineal ulceration. Inflammatory oedema, diffuse infiltration with lymphocytes and plasma cells and fibrinoid necroses of three capillaries are seen. Hematoxylin and eosin stain, 40:1 planachromatic objective lens.

FIG. 7. Case IV. Rectum. Patient with sigmoidostomy below which the mucosa is extremely atrophic with intense lymphocytic infiltration, whereas the inflammatory reaction in the other layers is inconspicuous. Hematoxylin and eosin stain.

gastrointestinal tract appeared to be normal. The small intestines were collapsed, with fibrous adhesions on the left side; there was no peritonitis. The mucosa of the large bowel was oedematous and displayed hyperplastic foldings but no ulcers. The sling supplying the colostomy was widely open and inflamed. The superior part of the non-functioning rectosigmoid sling appeared obliterated but the rectal ampulla was inflamed with numerous submucous haemorrhages and a necrotic fistula opening into the vagina. The liver was pale and fatty; the biliary passages were unobstructed.

Histological examination (including previous specimens): Examination of the uterine curettage performed in 1948 because of vaginal discharge revealed a slightly hyperplastic endometrium with nonspecific inflammatory infiltration with lymphocytes and plasma cells. Four biopsy specimens (1949–1953) from the non-healing perineal ulceration revealed nonspecific chronic inflammation with superficial necrosis and granulation tissue containing polymorphonuclears and a few giant cells, and underlying fibrosis with infiltrating lymphocytes and numerous plasma cells. The infiltrates were mostly pericapillary, whereas the arterioles and medium-sized veins appeared normal. Some capillaries exhibited endothelial degeneration and fibrinoid necrosis (necrotizing vasculitis, see Figure 6). A specimen from a papular eruption on the arm (1954) revealed atrophic epithelium, in places indistinctly demarcated, and recent obstructive capillary endothelial proliferation and acute inflammatory reaction in the superficial part of the corium.

At autopsy examination of the lungs revealed pus in some bronchioles and peribronchial chronic inflammatory reaction, but they were otherwise normal. The kidneys had a normal structure except for a slight focal fibrosis and a few hyalinized glomeruli. No vascular lesions, notably no "wireloops," were present. A few plasma cells were observed interstitially. The pancreas displayed a slight insular hyperplasia. The thyroid gland was normal. The adrenals appeared atrophic and devoid of lipoids. The spleen revealed a hyperplastic pulp with some plasma cells; the follicles were preserved. Some brownish pigment was positive for iron. The arterioles appeared somewhat thickened and fibrosed but without "onion peel" formation. The bone marrow was slightly hyperplastic

and contained a few plasma cells but no myeloma cells. Muscle tissue from the right psoas major was found to be normal.

Sections from the sigmoid colon revealed a massive mucosal infiltration with lymphocytes and plasma cells, with focal loss of epithelium and oedema of the submucosa. The rectum had an atrophic mucosa and slight fibrosis of the submucosa with only inconspicuous inflammatory reaction. (Fig. 7.) In the periproctal fat, however, minute infiltrates of lymphocytes were observed, predominantly around capillaries and venules but not surrounding arterioles or larger vessels. A very few capillaries displayed indications of fibrinoid necrosis. The liver showed a marked fatty degeneration and some infiltration with lymphocytes, but no cirrhosis or necrosis. A little pigment present was positive for iron.

COMMENTS

The four reported cases demonstrate that the gastrointestinal tract may be implicated in "the mucocutaneous-ocular syndrome." In three of the patients this was the primary cause of death, while one died from central nervous system involvement.

All the patients were middle-aged women. The duration of the disease varied from eight months to fifteen years; the course was markedly remittent although progressive. The various symptoms involving skin, mucous membranes, eyes and joints were not usually present at the same time. All our patients had previously been treated by specialists in different fields for their varying symptoms and signs before an adequate diagnosis was made.

The gastrointestinal lesions *per se* did not present any characteristic features indicative of their relation to the mucocutaneous-ocular syndrome. In Case IV in which the rectum was involved, the proctitis was initially considered to be secondary to the anogenital ulceration. In Case III in which autopsy revealed involvement of the whole gastrointestinal tract, although to a lesser degree than in the other cases, gastrointestinal symptoms were not noted at all. In Cases I and II, in which the disease involved the large bowel, the signs, including the rectoscopic picture, did not differ from that of a severe ulcerative colitis. Our four cases were observed within three years. This indicates that gastrointestinal involvement may be more common than generally recognized.

It is to be stressed that the intestinal symptoms and especially the rectoscopic picture in our patients could not be distinguished from those of ulcerative colitis. It is well known that skin eruptions, aphthous stomatitis and also eye lesions do occur in ulcerative colitis, but even in authoritative recent reviews [*24,37*] no connection with mucocutaneous-ocular syndrome is mentioned. Ustvedt [*38*], who recently studied the occurrence of ulcerative colitis in Norway during a ten-year period, did not record cases of this type. Even Goldgraber and Kirsner [*19*] who made a survey of "specific" diseases simulating ulcerative colitis did not include the mucocutaneous syndrome. To obtain an adequate diagnosis in the cases in which ulcerative colitis is a part of this syndrome one has to pay special attention to anogenital ulcers and other mucocutaneous and ocular lesions. One cannot, however, expect to find all these symptoms present at the same time, and therefore a careful case history is of utmost importance. In Cases I, II and IV the colitis was persistent while other symptoms and signs were transient.

An adequate diagnosis may have therapeutic consequences. The observations in Cases I and IV indicate impaired wound healing and in our opinion one has to be extremely reluctant to intervene surgically in cases like this. Furthermore, our cases have not convinced us of the beneficial effect of corticoid therapy. An initial favourable effect proved merely transient and in Case II an intestinal perforation was concealed.

We can add nothing to the etiology of this disorder. Extensive bacteriological and serological examinations were inconclusive. No attempt was made to culture viruses. Inclusion bodies indicative of a virus etiology were not observed in the histological specimens.

The autopsy findings of special interest in the cases herein described are those in the gastrointestinal tract, in combination with the pronounced cachexia present in all cases. The microscopic lesions were chiefly limited to nonspecific moderate chronic inflammatory reactions. Both in the lesions from the skin and in those from the intestines a tendency to pericapillary and perivenular localization of the mononuclear infiltrates was conspicuous. In some areas necrotizing vasculitis with associated fibrinoid necrosis was apparent. Such findings are otherwise characteristic of the so-called "collagen" diseases.

In a fatal case of Stevens-Johnson syndrome reported by Short [*34*] the histological findings

were those of periarteritis nodosa and Wegener's granulomatosis. Such lesions were not observed in our cases. Alexander and Cope [*2*] observed widespread necrosis of both arterioles and venules with fibrinoid necrosis of associated collagen, consistent with the findings in disseminated lupus erythematosus. France et al. [*18*] stressed the point that perivenular infiltrates are found in Behcet's syndrome. Our patient (Case III) had an atrophic oesophagitis with fibrosis of collagen of a type usually seen in scleroderma, another "collagen" disease.

SUMMARY

The designation, mucocutaneous-ocular syndrome, is used here as a general collective term to include Behcet's syndrome, severe erythema exudativum multiforme, Stevens-Johnson syndrome and ectodermosis erosiva pluriorificialis.

These syndromes sometimes involve internal organs. Usually the respiratory tract or the central nervous system is affected, but a review of the literature reveals that involvement of the gastrointestinal tract is not infrequent. Fatal cases have rarely been reported and very few of these have been due to gastrointestinal lesions.

We describe four fatal cases, all occurring in women, with involvement of the gastrointestinal tract. In two cases the main lesions were in the large bowel associated with a clinical picture of ulcerative colitis. In one case the lesions were confined for the most part to the rectum and in one case histological examination revealed that all of the gastrointestinal tract was involved. The microscopic findings were chiefly limited to moderate nonspecific inflammatory reactions surrounding capillaries and venules.

Gastrointestinal involvement in the mucocutaneous-ocular syndrome apparently is not rare. Presumably, some cases ordinarily included in the large group of ulcerative colitis actually belong to this syndrome. Sigmoidoscopy will not suffice to separate these cases from ordinary ulcerative colitis, but a case history of exanthemata, recurring stomatitis, anogenital ulcers and involvement of the eyes may be diagnostic.

Our experience in two cases indicates impaired wound healing in this disorder, which suggests caution in surgical intervention.

Acknowledgment: Our thanks are due to Torbjørn Elgvin, M.D., Bodø sykehus, for his kind permission to use the clinical case report on Case III.

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An Appraisal of Fulminant Meningococcemia with Reference to the Shwartzman Phenomenon*

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MANY of the pathological manifestations of meningococcemia have never been satisfactorily explained, either as a direct effect of the bacterium or as an effect of its endotoxin. More specifically, the greatest interest has concerned the purpuric skin lesions which the majority of patients show, and the occurrence of the Waterhouse-Friderichsen syndrome (here defined as bilateral adrenal hemorrhage in a patient with fulminant septicemia) in approximately 3.3 per cent of individuals with infection due to Neisseria meningitidis [*1*]. It has been proposed that the purpuric manifestations may be attributable to the Shwartzman phenomenon, whereas such a mechanism has been denied in the Waterhouse-Friderichsen syndrome [*2,3*]. Black-Schaffer in 1947, for example, reasoned that the apparent absence of bilateral renal cortical necrosis in patients with the Waterhouse-Friderichsen syndrome gave no support to the idea that the adrenal hemorrhages are ascribable to a generalized Shwartzman reaction. He has, however, since observed one case of meningococcemia with bilateral renal cortical necrosis [*4*]. Renal damage of this type has been considered to be the characteristic [*5–8*] if not specific [*9*] lesion of the generalized Shwartzman reaction by most observers.

The Waterhouse-Friderichsen syndrome is not restricted to meningococcemia but may be seen in a variety of bacterial infections, particularly with gram-negative organisms such as Escherichia coli and Hemophilus influenzae, and less frequently in pneumococcal, staphylococcal and diphtherial disease [*10,11*]. The great tendency to such adrenal involvement in meningococcemia, however, is striking.

Our purpose has been to study reports of a relatively large series of cases from one institution, with the object of evaluating the evidence for and against the operation of the Shwartzman phenomenon (local or generalized) in meningococcemia. The opportunity to do this has been afforded by the seemingly high endemicity of N. meningitidis in Greater Cincinnati. The material to be presented is not intended to cover all aspects, clinical or pathological, of meningococcal infection in children.

MATERIAL AND OBSERVATIONS

In the twenty year period 1937 to 1956, fifty-two fatal cases of meningococcic infection were seen at the Cincinnati Children's Hospital; forty were examined at autopsy. The meningococcus organism was identified by culture or smear in thirty-four of these forty, in the remaining six the classic features of the Waterhouse-Friderichsen syndrome were present at autopsy, as well as the typical purpura of meningococcemia. Four of the latter six patients were receiving antibiotic therapy before admission to the hospital; two were not examined bacteriologically. Eight patients who came to autopsy were dead on arrival. In the twelve fatal cases in which no autopsy was performed meningococcemia was eventually proved to be present. These 52 fatal cases were compared with 152 consecutive bacteriologically proved cases in which the patients survived, all seen within the seven year period 1949 to 1956.

The age and sex analysis of the series is given in Table 1. The age range was three weeks to fifteen years, with only a trend (of borderline significance) of greater severity of the disease in patients under the age of two years. The female mortality rate of 34 per cent was significantly higher than the male mortality rate of 19 per cent (probability less than 2 per cent).

The patient's condition on admission was evaluated with respect to evidence of shock, as indicated by

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TABLE I
AGE AND SEX DISTRIBUTION OF 204 PATIENTS

Status of Patient	Age		Sex	
	<2 yr.	>2 yr.	Male	Female
Dead	34	18	22	30
Living	73	79	93	59
Total	107	97	115	89
	p = <.05		p = <.02	

TABLE II
MORTALITY IN RELATION TO CONDITION ON ADMISSION
204 PATIENTS WITH MENINGOCOCCEMIA

Status of Patient	In Shock on Admission		Dead on Arrival		Not in Shock on Admission		Total	
	No.	%	No.	%	No.	%	No.	%
Dead	26	50	8	15.4	18	34.6	52	25.5
Survived	4	2.6			148	97.4	152	74.5
Total	30	14.7	8	3.9	166	81.4	204	100.0

blood pressure determinations, and the state of the peripheral circulation, or both. The data, as shown in Table II, are thus both retrospective and subjective. In other respects, except for the white blood count, there was little clinical or laboratory difference, on admission, between patients who survived and those who eventually died. A summary of the laboratory examinations is presented in Table III.

There was great variation in treatment and, since virtually all patients received intensive antibacterial therapy, only the use of adrenal steroids is evaluated. Sixty-three patients received some form of adrenal steroid. Considering only the 166 patients who were not presumed to be in shock at the time of admission, the data in Table IV show a striking difference in outcome; patients receiving steroid therapy had a mortality of 21 per cent compared with a 7 per cent mortality in those not so treated. There was nothing in the clinical records to suggest that of the patients not in shock, the forty-three who were treated with steroids appeared more ill, as a group, than the 123 patients who were not treated in this manner; the institution had no definite policy on the use of adrenal steroids during the period of study. It is evident, however, that the state of shock was a strong inducement for steroid treatment since, of the forty-four fatal cases in which the patients were not dead on arrival to the hospital, some adrenal supplement was given in thirty-four.

Sections of skin were available for histologic examination in twenty-six of the autopsy cases. The findings are shown in Table V. The three notable features in the skin were the occurrence of loosely aggregated venular thrombi, a generally slight or even absent acute vasculitis, and the absence of an acute dermal inflammatory reaction, in association with the thrombi. (Fig. 1.) In only one instance were there lesions characteristic of necrotizing vasculitis, and these were located in the subcutaneous tissue. (Fig. 2.) The latter lesions could be expected to be the basis of local gangrenous changes, which occasionally occur as a sequel to meningococcemia.

The adrenal glands were examined in all forty autopsy cases and were considered to be typical of the Waterhouse-Friderichsen syndrome in all but four cases, in which purulent meningitis was the cause of

TABLE III
SELECTED LABORATORY FINDINGS ACCORDING TO OUTCOME

Laboratory Finding	Fatal Cases		Surviving Cases	
	Value	No. in Which Determined	Value	No. in Which Determined
White blood cell count*†	<10,000	15	<10,000	30
	>10,000	11	>10,000	121
Hemoglobin*‡	10.2 gm. (Av.)	24	10.5 gm. (Av.)	152
Non-protein nitrogen*	54 mg. % (Av.)	23	38 mg. % (Av.)	65
Co_2*	15.4 mM./L. (Av.)	17	22 mM./L. (Av.)	66
Cl^-*	103.4 mEq./L. (Av.)	33	100.5 mEq./L. (Av.)	66

* First value recorded.
† Significance of difference in white blood cell count between fatal and surviving cases p = <.01.
‡ Colorimetric.

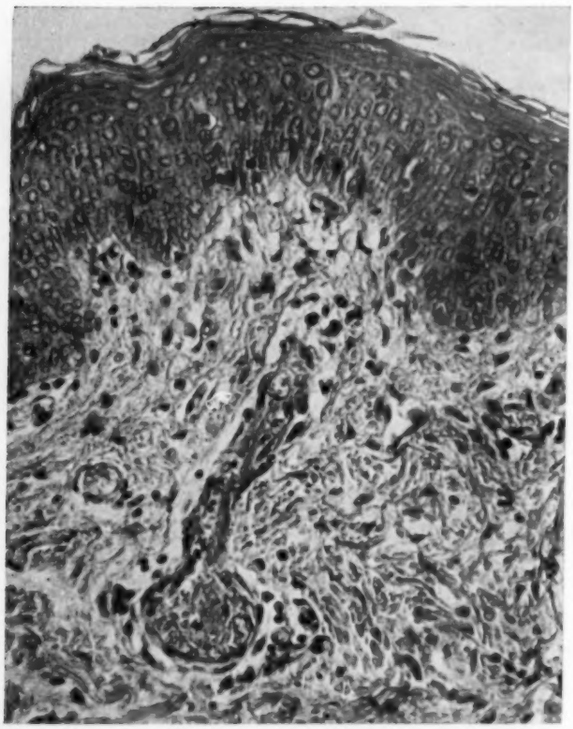


FIG. 1. Skin, showing venule thrombus characteristic of meningococcemia. Note the fibrin clump with blood cells loosely aggregated in and about it and the thin wall of the vessel without evidence of a vasculitis. C-51-51. Hematoxylin and eosin.

death. However, the fact that hemorrhage was massive in twenty-two cases precludes analysis of the various components of the lesion. There were, however, certain features of interest. In the more intact areas, or in apparently early lesions, the familiar degenerative changes seen in septicemia, particularly the so-called pseudotubular degeneration of Rich, were observed [*12*]. (Fig. 3.) The most notable feature was the occurrence of sinusoidal thrombosis which was seen sufficiently often, independent of hemorrhage, to give the impression that it was the basis of such hemorrhage. (Fig. 4.) The thrombi were variable in location but tended to be in the inner cortical or medullary sinusoids. We were never convinced that there was significant evidence of primary vascular damage to the sinusoids, although focal adrenalitis was present in thirteen cases (severe in three) and diffuse adrenalitis was present in two cases. The infarct-like character of the early focal hemorrhagic lesion is unmistakable, and it is our opinion that total involvement of the adrenal represents a form of massive or confluent infarction.

Sections of kidney were available for study in all forty autopsy cases. Thrombi, either glomerular, intertubular capillary, or both, were observed in nine instances. In three patients there was also bilateral cortical necrosis, well marked in two, and in an early

TABLE IV
MORTALITY IN RELATION TO STEROID THERAPY
PATIENTS NOT IN SHOCK ON ADMISSION

Patients (No.)	Steroid Therapy	Mortality (%)
43	Yes	21
		$p = <0.02$
123	No	7

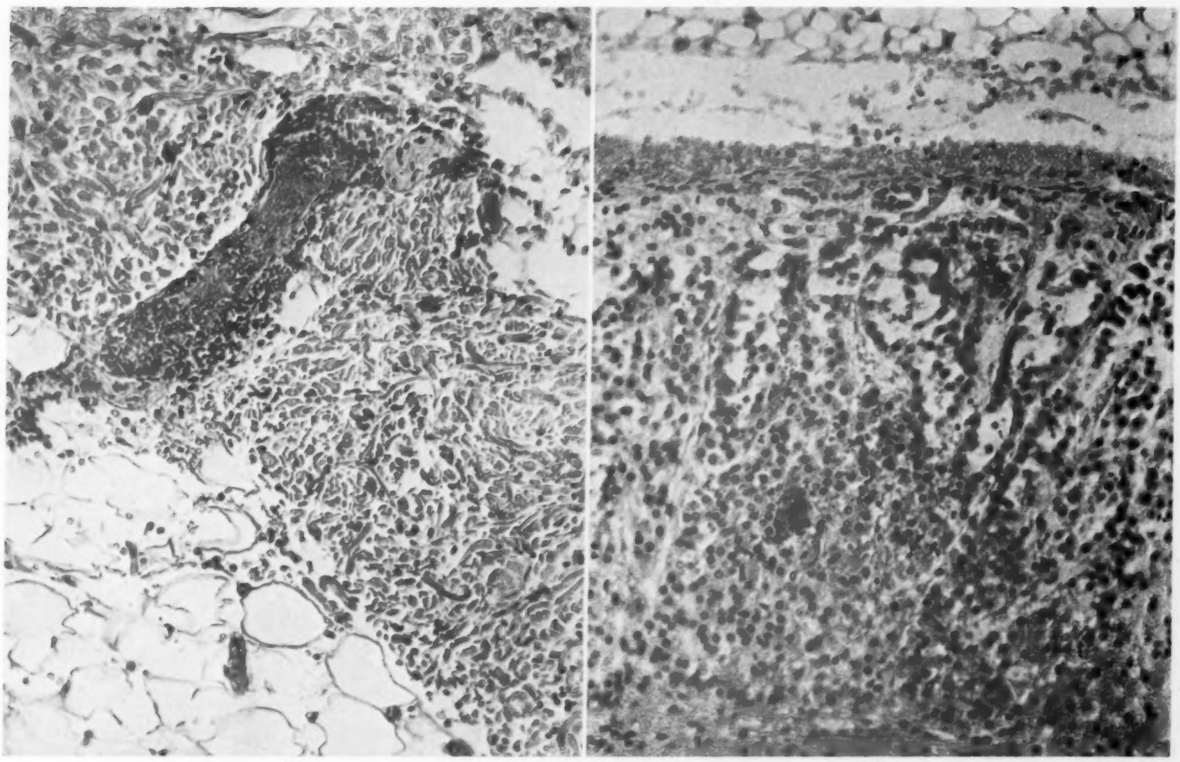
TABLE V
HISTOLOGICAL FEATURES OF SKIN LESION IN TWENTY-SIX PATIENTS

Type of Alteration	Specimens in Which Present (No.)
Loosely aggregated thrombi in venules and capillaries	22
Pure fibrin thrombi	2
Angiitis and periangiitis	
Slight	13
Moderate	3
Necrotizing vasculitis	1
Perivascular hemorrhage	7

stage in the third. (Figs. 5 and 6.) In only two cases was acute interstitial nephritis seen, in both instances distinctly focal. In a review of the clinical data it was found that the three patients with renal cortical necrosis were not in shock at the time of admission to the hospital, and received some form of adrenal cortical steroid prior to the development of shock. These cases are briefly summarized in Table VI.

COMMENTS

Comparison of the skin lesions of meningococcemia in man with the experimentally produced localized Shwartzman reaction in the rabbit reveals certain striking differences. Notably, the experimental lesion shows a conspicuous exudation of acute inflammatory cells in the dermis, and an acute vasculitis following the provoking injection of endotoxin [*13–16*]. However, there is similarity of the loosely aggregated venular thrombi in the dermis in lesions in man to the venular thrombi in the experimental lesion seen following the provoking injection of endotoxin. Such dermal thrombi in the human subjects studied were not necessarily associated with any visible evidence of vasculitis and, when present, the dermal vasculitis was seldom of more than minimal severity.



2 3

FIG. 2. Necrotizing vasculitis at the subcutaneous-dermal junction. Numerous small arteries in the deeper subcutaneous tissues were similarly involved. C-51-5. See Case III in Table VI. Hematoxylin and eosin.

FIG. 3. Adrenal gland showing pseudotubular degeneration as described by Rich. C-49-51. Hematoxylin and eosin.

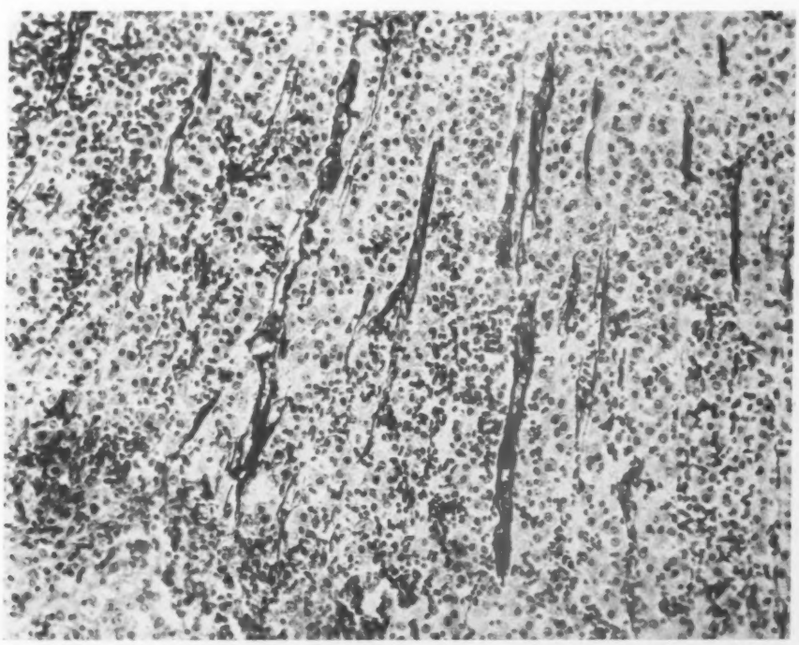
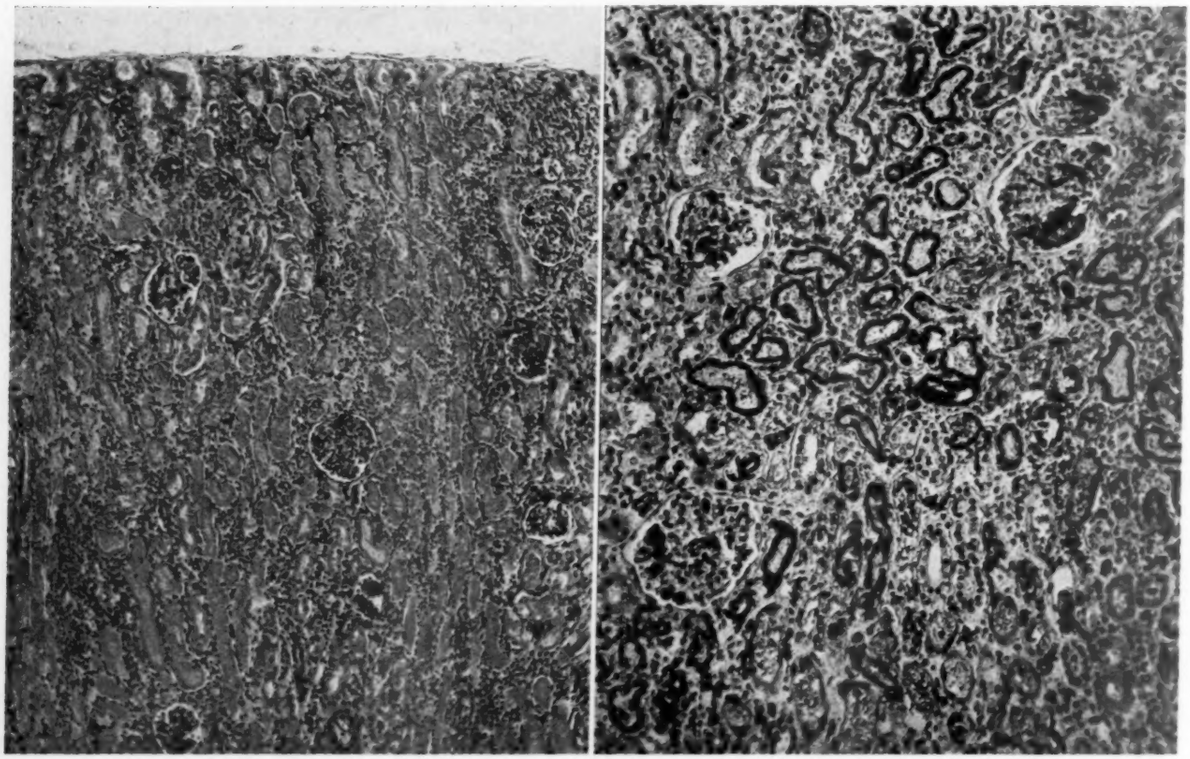


FIG. 4. Adrenal gland showing sinusoidal thrombi and degenerative changes. In the sections examined this was the only area not markedly distorted by massive hemorrhage. C-50-99. Phosphotungstic acid, hematoxylin.



5 6

FIG. 5. Kidney showing cortical necrosis. Note the widespread total necrosis of convoluted tubules. Glomerular capillary thrombi are not distinguishable at this magnification. C-50-88. Hematoxylin and eosin.

FIG. 6. Kidney showing glomerular capillary thrombi. Note also the group of necrotic convoluted tubules. The degree of necrosis varied from very slight in some areas to moderately advanced in others. Case of early, bilateral cortical necrosis. C-51-5. See Case III in Table VI. Phosphotungstic acid, hematoxylin.

There is no well studied experimental counterpart to the adrenal hemorrhage seen in the Waterhouse-Friderichsen syndrome. We have already mentioned the observation that thrombotic manifestations in the sinusoids of the adrenal are frequent in meningococcemia in man, and appear to precede hemorrhage. The simple mechanical explanation, of loss of support of the sinusoids as a result of necrobiotic changes in the parenchyma, seems to us a pathogenetically inadequate explanation of the adrenal hemorrhage seen in the Waterhouse-Friderichsen syndrome [*17,18*]. Further, there is no anatomic evidence to suggest primary vascular injury. It is well known that the Waterhouse-Friderichsen syndrome is not limited to meningococcemia, being seen in a variety of infections due to gram-negative organisms, particularly the coliform group, and occasionally to gram-positive organisms. We have examined the adrenal glands of a number of patients with fulminant septicemia due to a variety of organisms, such as the coliform bacilli and H. influenzae and in several instances have observed sinusoidal thrombi, with and without associated hemorrhage, similar to the lesions described in the meningococcemic cases.

There is no need to make a detailed anatomic evaluation of the renal lesions of cortical necrosis, since there are numerous reports dealing with this [*19–21*]. Rather, the concern of this discussion will be with the significance of the lesion. We are unaware of any previous report describing the occurrence of renal cortical necrosis in meningococcemia. On the other hand, the occurrence of capillary thrombi, particularly in glomeruli, in autopsy cases of fulminant meningococcemia is well known and such lesions in the absence of cortical necrosis were seen in several of the cases of this series [*22*].

The occurrence of three instances of renal cortical necrosis in this series is of special interest. The anatomic conformity of the lesions to those of the generalized Shwartzman reaction,

TABLE VI

CASE SUMMARIES OF MENINGOCCOCEMIC PATIENTS WITH BILATERAL RENAL CORTICAL NECROSIS

Data	Case I; C-55-122; C. H., 1 year old white girl	Case II; C-50-88; C. K., 1¼ year old white girl	Case III; C-51-5; S. S., 3¾ year old white girl
Onset	4 hours prior to admission	2 hours prior to admission	11 hours prior to admission
Symptoms	Fever and anorexia, petechial rash on sponging	Fever, ecchymotic rash	Vomiting, chills and fever, rash ½ hour prior to admission
Findings on first examination	Blood pressure, 80/40 mm. Hg.; temperature, 102°F, (rectal); pulse 80; neurological examination negative	Blood pressure 70/30 mm. Hg.; temperature 106°F. (rectal); alert, no meningeal signs.	Blood pressure 80/40 mm. Hg; pulse 160; temperature 104°F. (rectal); semidelirious; no meningeal signs
Laboratory findings	Hemoglobin 5.2 gm.; white blood count 4,450 with 54% polymorphonuclear leukocytes; cultures of blood, nasopharynx and cerebral spinal fluid grew N. meningitidis; lumbar puncture; normal chemistry, no cells	Hemoglobin 9.7 gm.; white blood count 36,000 with 87% polymorphonuclear leukocytes; urine −2 + albumin; lumbar puncture normal; cultures of blood and nasopharynx grew N. meningitidis	Hemoglobin 11.2 gm.; white blood count 3,000 with 76% polymorphonuclear leukocytes; petechial smear: gram-negative diplococci; blood culture grew N. meningitidis
Treatment	Immediately started on sulfadiazine, penicillin and Cortef® in large dosage; 75 ml. whole blood	Started on sulfadiazine, penicillin and adrenal cortical extract in large doses 75 minutes after admission	Immediately started on intravenous sulfadiazine, penicillin and adrenal cortical extract and cortisone in large dosage
Course	Blood pressure stable at 80 systolic until just before death. Progressive deterioration; total urine output 32 ml.; death 55 hours after admission	Blood pressure maintained at 70/40 for 24 hours; then progressive deterioration; total urine output 43 ml.; death 33 hours after admission	11 hours after admission had massive hematemesis and hematuria; given 500 ml. fresh whole blood; blood pressure stable (80/40–105/70) for 28 hours, then became unobtainable; given 100 ml. whole blood with recovery of blood pressure until death 8 hours later, 36 hours after admission; total urine output 432 ml. (bloody)
Anatomic diagnoses	Bilateral renal cortical necrosis; Waterhouse-Friderichsen complex; cutaneous venule thromboses (purpura of meningococcemia); serosal, visceral and cutaneous hemorrhages; aspiration of gastric contents; bone marrow compatible with megaloblastic anemia	Bilateral renal cortical necrosis; Waterhouse-Friderichsen complex; cutaneous venule thromboses; serosal, visceral and cutaneous hemorrhages; focal myocarditis; edema of the brain	Early bilateral renal cortical necrosis; Waterhouse-Friderichsen complex; cutaneous venule thromboses; serosal, visceral, cutaneous and cerebral hemorrhages; gangrene of finger tips; hemorrhage of the lungs

produced experimentally in rabbits, is close. The unexpected finding of a possible correlation between the administration of an adrenal cortical steroid, and the development of the lesion, seems of particular importance. It is known that the use of cortisone is one of the most efficient methods of potentiating the Schwartzman phenomenon, local or general, and, in fact, in an animal thus treated a preparatory injection of endotoxin is unnecessary for eliciting the reaction [*7,23–26*]. It is possible to conclude that the three instances of renal cortical necrosis herein cited are manifestations of a generalized Shwartzman reaction, and that the purpuric lesions of the skin and the adrenal lesions are related phenomena.

From this viewpoint, the skin lesions can be interpreted as local Shwartzman reactions. The simplest explanation is that the skin sites become prepared in the early bacteremic (or toxic) phase of the infection, and that provocation results from continuing bacteremia (or toxemia). On the basis of certain experimental observations, however, the credibility of this explanation is suspect. There is, for example, the phenomenon of resistance, which is induced by

multiple rather closely spaced injections of the eliciting material, a situation perhaps analogous to the clinical one [*27,28*]. Recent data show the dependence of this phenomenon on the reticuloendothelial system and a complex relationship of time and dosage [*29*]. If the conditions of meningococcic infection in human subjects do favor the development of resistance, the skin lesions cannot be readily explained on the basis of the local Shwartzman reaction. With present information, however, there is no way to assess the possibility of resistance in human meningococcemia. A recent study on the tissue content of lipopolysaccharides with Shwartzman activity is of considerable interest in that rabbit skin is lacking in such activity, while the kidney content is high, observations which may be of direct importance [*30*]. It is difficult to understand why septicemia should favor the localized Shwartzman reaction but not the generalized Shwartzman reaction. Using standard technics in the rabbits, both forms of the phenomenon require a stage of preparation which would make any assumption that a given tissue is or is not in a state of Shwartzman preparation by virtue of its content of Shwartzman-active material unreasonable. Possibly the tissue content of such material is related, however, to some undefined natural state of resistance to manifestation of the reaction on provocation. Another factor to be considered is the absence of an acute exudate of polymorphonuclear leukocytes in the dermis in the lesion in man, an occurrence which is believed to be essential to the development of the experimental Shwartzman reaction [*13–16*]. There is no absolute proof that the presence of polymorphonuclear leukocytes, presumably the source of a high molecular weight polymerized polysaccharide needed for the reaction, is essential to the development of the local Shwartzman reaction, although it does not occur in animals with leukopenia induced by the administration of nitrogen mustard [*31–33*].

The adrenal lesion can also be conceived as a local Shwartzman reaction. To be accounted for is the unusual liability of patients with meningococcemia to adrenal involvement. This might in part be related to the high Shwartzman potency of meningotoxin. However, it is also possible that the adrenal damage is in some way related to a stress phenomenon, and in this sense is an accident of circumstance due to the high local level of cortical steroids. No experiment has analyzed this possibility, although potentiation of the generalized Shwartzman reaction by ACTH has been studied [*7*]. It is perhaps pertinent that the rabbit, in which the majority of studies on the Shwartzman phenomenon have been made, does not respond to the administration of ACTH in the same fashion as the human subject. Rats differ sharply from rabbits in this same regard. Even with chronically administered high doses of ACTH, the rabbit does not show the expected clinical picture of adrenal hyperfunction and, indeed, the adrenal gland itself does not show a demonstrable ACTH effect. In contrast, given cortisone the rabbit loses weight, frequently has coryza, exhibits lipemia and may die without obvious cause [*34,35*]. This could mean that rabbits do not respond well to the administration of commercial ACTH or possibly that they are relatively unresponsive to ACTH in general. The rarity of a Waterhouse-Friderichsen lesion in meningococcic infection of rabbits [*2*] may be related to failure of the adrenal to respond to ACTH. The dependency on hormonal stimulation for the production of adrenal hemorrhage in the guinea pig by diphtherial toxin has been demonstrated by Tonutti [*36*]. On the other hand, his experiments have not shown this dependency in the case of Esch. coli pyrogen and meningococcal toxin. Tonutti's experimental conditions, however, particularly the high dosage of toxin used, suggest the operation of other mechanisms than the Shwartzman phenomenon.

The material presented cannot be taken as proof of the operation of the Shwartzman phenomenon in meningococcemia in man, but the implications are strong that such is the case. At the present time the administration of adrenal cortical steroids, on the assumption of replacement therapy, is popular, although several reports question whether or not steroids have altered the outcome of the Waterhouse-Friderichsen syndrome [*37,38*]. A point to be emphasized is the lack of physiological evidence of acute adrenal insufficiency in the patient with fulminant meningococcemia [*38*]. The similarity of the clinical sequence of events in the three fatal cases of meningococcemia with bilateral renal cortical necrosis reported here, to those of deliberate experimental design, are close enough to imply that a deleterious rather than a beneficial effect may result on occasion from the use of adrenal steroids in such patients.

SUMMARY

In three of fifty-two fatal cases of meningococcic infection bilateral renal cortical necrosis developed under circumstances suggesting a direct relationship to adrenal steroid therapy. This occurrence, and the apparent causal relationship of thrombosis in the production of the hemorrhagic lesions of the skin and adrenals in the Waterhouse-Friderichsen syndrome, suggest that the Shwartzman phenomenon may be responsible for certain manifestations of fulminant meningococcemia. The apparent rarity of renal cortical necrosis in meningococcic infection in human subjects, a lesion that is characteristic of the generalized Schwartzman reaction in rabbits, suggests that the common skin and more occasional adrenal lesions of this disease may be produced by the local Shwartzman phenomenon.

The analysis of the fifty-two fatal cases and a comparison with 152 cases in which the patients survived raises a question of the wisdom of adrenal steroid therapy in fulminant septicemia.

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Pseudomonas Septicemia*

Observations on Twenty-three Cases

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WITH the advent of potent antibiotics and other new drugs, the role of Pseudomonas aeruginosa as an infectious agent in man has become more important [*1–4*]. Only scattered reports are available, however, describing pseudomonas septicemia and its response to contemporary antimicrobial agents, and on this account the following observations on the clinical, therapeutic and morphologic aspects of pseudomonas septicemia appear to be timely. In a later communication [*5*] the broader aspects of infection with this microorganism will be considered and the literature reviewed.

The files of the Bacteriology Department of the Clinical Center were reviewed for patients with blood cultures positive for Ps. aeruginosa. An examination was then made of the clinical charts and reports of the postmortem cultures of this group. Most of the patients had been observed daily and treated by one or more of us. Autopsies were performed in all of the twenty-two fatal cases.

Thirteen of the twenty-three patients were from the acute leukemia service of the National Cancer Institute and were selected for special presentation and comparison of certain data because their clinical management was similar. Bacteriological technics were performed as described in a previous publication [*6*].

The following three cases, briefly referred to in Table 1, have been selected for detailed presentation:

CASE REPORTS

CASE 1. C. B., a thirty-two year old white man with acute lymphocytic leukemia, had been treated with methotrexate for fifty days without remission. Because of fever of unknown origin he was admitted to the Clinical Center on June 14, 1956, and was given penicillin and streptomycin, with improvement.

On August 6 fever recurred. The subsequent changes in temperature and laboratory values are illustrated in Figure 1. On August 9, a blood culture was negative, and liver function tests were within normal limits. A small fissure was noted between the fourth and fifth toes of the right foot, and the fifth toe was slightly red and swollen. Pink, oval macules were noted on the thorax and upper part of the abdomen, measuring 0.5 to 1.0 cm. in diameter. These were non-pruritic and blanched on pressure. The following day Ps. aeruginosa was cultured from the blood and was one of several microorganisms isolated from the lesion in the foot. Lymphangitic streaking was noted on the affected foot and ankle. The macules on his trunk persisted. For the next four days daily blood cultures were positive for Ps. aeruginosa. Penicillin and streptomycin were discontinued and he was given tetracycline and later polymyxin and dihydrostreptomycin. The right foot became grossly swollen, with increasing lymphangitis followed by femoral lymphadenitis. The patient became tremulous, sweaty, and appeared acutely "toxic." The fifth toe became black and necrotic, deep tendon reflexes became hypoactive, and shock supervened. On August 14, the day before death, jaundice occurred and metastatic abscesses appeared. The toe lesion had a serous exudate, and the foot veins became thrombosed. Gallop rhythm and moderate abdominal distention developed. The patient complained of generalized body stiffness. Terminally he became deeply jaundiced and confused, and died in irreversible shock six days after the appearance of the interdigital fissure.

At autopsy, the clinical findings were confirmed. Microscopic examination of lymph nodes, liver, bone marrow, spleen, thymus and faucial tonsils revealed lymphocytic leukemia infiltrates. Both lungs were diffusely hemorrhagic and partially consolidated. Microscopic sections from all lobes revealed scattered,

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TABLE 1

A LIST OF THE MAJOR FINDINGS AND COMPLICATIONS OF PSEUDOMONAS SEPTICEMIA IN TWENTY-THREE PATIENTS

Patient, Age (yr.) and Sex	Diagnosis	Pseudomonas Cultures	Portal of Entry	Survival (days) after Onset of Septicemia	Associated Findings	Terminal Events	Autopsy Cultures (Pseudomonas)	Relevant Postmortem Findings
J. B., 11, F	Acute myelogenous leukemia	Blood, buttocks abscess	Same	4	.....	Dyspnea, cyanosis, gallop rhythm, seizure	Heart blood, lung, pericardial fluid	Bacillary cellulitis, buttocks; hemorrhagic pneumonia
A. D., 4, M	Acute lymphocytic leukemia	Blood, groin abscess	Same	3	.....	Acutely "toxic"—died during exchange transfusion	Heart blood, pericardial fluid, femoral lesion	Bacillary cellulitis, femoral subcutaneous tissue; hemorrhagic bacillary pneumonia
A. C., 22, M	Acute lymphocytic leukemia	Blood, sputum	Periodontal abscess	1	Skin lesions	Tracheotomy for respiratory stridor, gastrointestinal bleeding, heart failure, shock	Lung, buccal mucosa	Extensive bacillary vasculitis and gangrenous changes, tongue, oral mucosa, and proximal esophagus; hemorrhages, lungs and esophagus
S. G., 3, F	Acute lymphocytic leukemia	Blood, iliac bone marrow site	Same	3	Jaundice, diarrhea	Rales, semicoma, cyanosis, rapidly spreading lesions	Heart blood, peritoneal fluid	Bacillary cellulitis, inguinal and abdominal subcutaneous tissue; hemorrhagic pneumonia
A. G., 34, F	Chronic lymphocytic leukemia	Blood, sputum, nose, pharynx	Face abscess	2	Skin lesions, meningitis	Metastatic abscesses, disorientation, semicoma	Meningeal exudate	Multiple abscesses involving heart, liver, spleen, pancreas, duodenum, jejunum, thyroid gland, kidneys, skin of face; acute purulent meningitis
L. E., 61, F	Carcinoma ovary	Blood	Gastrointestinal tract	3	Jaundice	Mental depression, gallop rhythm, pulmonary edema, shock	Heart blood, cellulitis left thigh	Bacillary cellulitis, left thigh; pseudomembranous colitis, perforation of sigmoid colon
C. B., 32, M	Acute lymphocytic leukemia	Blood, toe fissure	Same	5	Skin lesions, jaundice	Generalized tremor, gallop rhythm, metastatic abscesses, refractory hypotension	(Heart blood sterile)	Bacillary cellulitis, foot and leg; mycotic and mixed bacterial abscesses, lungs
A. S., 37, M	(?) Malignant lymphoma	Blood, throat, sputum, gastric washings	Tonsil or lung	3 4	Skin lesions, jaundice	Apprehension, ascites, coma	Heart blood	Multiple intravascular foci of thrombosis and bacilli involving all parts of the body examined, septic thrombi and microinfarcts, multiple, brain
N. E., 37, F	Chronic myelocytic leukemia	Blood, cerebrospinal fluid, mouth, throat	Oral mucosa	7	Arthritis, skin lesions, jaundice, meningitis	Delusions, disorientation, gallop rhythm, shock (coma), meningitis	Heart blood, synovial fluid (from right knee)	Multiple intravascular septic thrombi and multiple microabscesses involving kidneys, heart, lungs, liver, spleen; Janeway spots, hands, pyogenic arthritis, left hip, bacillary meningitis
H. K., 39, F	Chronic lymphocytic leukemia	Blood, nose, throat, sputum	Lung	9	.....	Pneumonia, anasarca, disorientation, coma	Not done	Septic thrombi, right ventricle and left atrium, heart; septic thrombosis, left pulmonary artery and vein; septic emboli, brain, thyroid gland, heart, lungs, kidneys, and retroperitoneal adipose tissue
B. H., 68, M	Acute myelogenous leukemia	Blood, perianal abscess	Perianal or face abscess	10	Skin lesions, jaundice, meningitis	Disorientation, paranoia, generalized tremors, incontinence, hypotension	Lung, rectum	Hemorrhagic pneumonitis, bacillary meningitis, bacillary abscesses, kidneys, bacillary proctitis
G. G., 6 mo., M	Acute disseminated histoplasmosis	Blood, ascitic fluid	Peritoneum (laparotomy or paracentesis)	3	Jaundice	Edema, gastrointestiinal bleeding, abdominal distention; acutely toxic	Heart blood, chest swab	No morphological lesions of pseudomonas seen; disseminated histoplasmosis
E. T., 3, M	Acute lymphocytic leukemia	Blood, throat	Throat or femoral catheter	5	Jaundice, meningitis	Convulsions, (?hypertensive), coma, gastrointestinal bleeding, rales, hypotension	Heart blood (staphylococci also present)	Meningitis; bacillary vasculitis, tongue, lungs, larynx, esophagus

TABLE I (*Continued*)

A LIST OF THE MAJOR FINDINGS AND COMPLICATIONS OF PSEUDOMONAS SEPTICEMIA IN TWENTY-THREE PATIENTS

Patient, Age (yr.) and Sex	Diagnosis	Pseudomonas Cultures	Portal of Entry	Survival (days) after Onset of Septicemia	Associated Findings	Terminal Events	Autopsy Cultures (Pseudomonas)	Relevant Postmortem Findings
A. S., 58, F	Acute lymphocytic leukemia	Blood	Perineal abscesses	1	Skin lesions, jaundice, meningitis	Cyanosis, twitching, generalized tremor, gallop rhythm; pulmonary edema	Spinal fluid	Mycotic abscesses (candida), lungs; no definite bacillary lesions
B. S., 9, F	Acute lymphocytic leukemia	Blood, throat, stool, labia, vagina	Tonsils or labial ulcer	2	Green stools	Rales, dyspnea, disorientation	Heart blood, lung	Bacillary vasculitis and ulceration, tonsils, intestine
M. M., 1, M	Acute lymphocytic leukemia	Blood, throat	Throat	5	.....	Blurred discs, gasping respiration, very "toxic"	Peritoneum, lung asbcess, lung (heart blood negative)	Bacillary vasculitis, tonsils and tongue; hemorrhagic pneumonia
J. K., 63, M	Mycosis fungoides	Blood, sputum	Lung or pharynx	4	Skin lesions	Hemoptysis, bronchopneumonia	Heart blood, lung	Mixed bacterial and fungal (candida) infections; cutaneous ulcers (postradiation); lungs; microabscesses mixed flora; microabscesses (coccal), brain and thyroid gland
A. M., 8, M	Granulomatous disease	Blood, urine	Leg ulcers or urinary tract or groin node	5	.....	Convulsions, hematomesia, cyanosis, heart failure, coma	Heart blood, subphrenic abscess, kidney, lung, spleen, skull burr holes	Disseminated granulomatous disease, etiology unknown, involving lungs, liver, spleen, kidneys, bone marrow, urinary bladder; chronic inguinal ulcer, skin; encephalomalacia and chronic meningitis
S. R., 54, M	Sarcoma nasopharynx	Blood, tumor of face, urine	Face tumor	2	Jaundice	Hemorrhage from tumor site	Heart blood	Ulceration, hemorrhage and bacillary vasculitis, nasopharynx; hemorrhagic pneumonitis
C. S., 4, M	Acute lymphocytic leukemia	Blood, stool, knee joint	?	6	Skin lesions, jaundice, arthritis	Localizing neurological signs, lethargy, abdominal distention, coma, shock	Heart blood, lung abscess liver abscess, pericardial fluid, joint fluid	Multiple bacillary abscesses, lung, liver, kidneys, middle ear, lymph nodes; pseudomonas appendicitis, meningitis, probably due to staphylococci
N. B., 17, M	Acute lymphocytic leukemia	Blood, stool	Gastrointestinal tract	4	Jaundice	Green stools, apprehension, tremors, agitation, abdominal distention, facial paralysis, shock	Spinal fluid (heart blood negative)	Hemorrhagic colitis; meningitis, hemorrhagic cerebellar, hemorrhagic pneumonia; ecthyma gangrenosa
R. M., 4, F	Acute myelogenous leukemia	Blood, urine; nose	Nose	7	.....	Abdominal distention, nonliasis, mucopurulent discharge from nose	Heart blood (pure), sacrum, bowel, middle ear, paranasal sinuses, eye, nose, lip	Ethmoid sinusitis, right otitis media; bilateral conjunctivitis; subcutaneous abscess, sacrum; ulcerative laryngitis and esophagitis; acute ulcers, colon
E. L., 54, F	Carcinoma of cervix	Urine	Ureter	Survived	Hypotension lethargy	.....	.....	.....

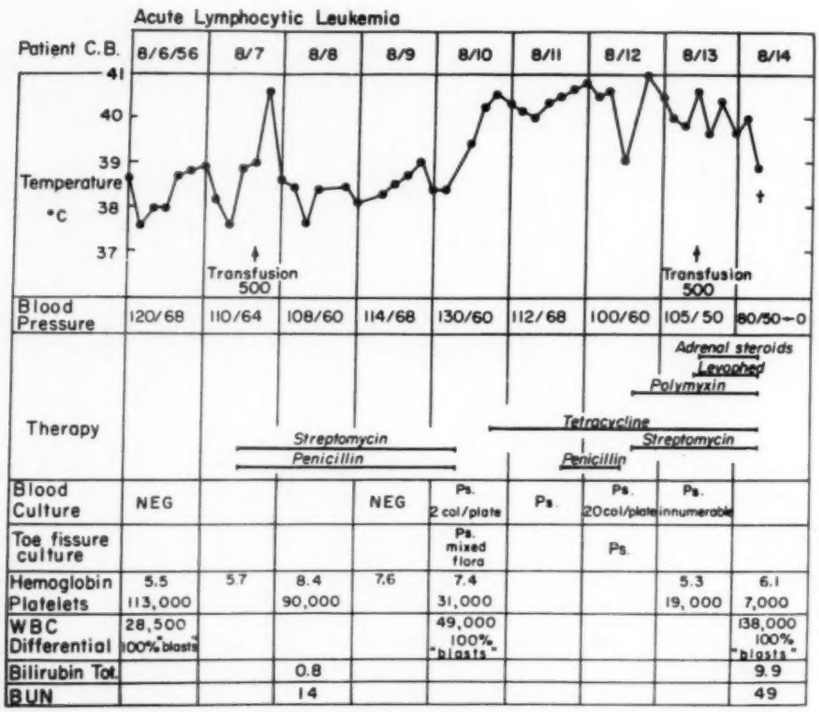


FIG. 1. Case I. Fatal course of acute pseudomonas septicemia.

sometimes confluent areas of acute hemorrhage and embolic pneumonia. Septic emboli were present in some pulmonary capillaries and veins. The diagnoses at autopsy were: acute lymphocytic leukemia; cellulitis, right foot; organizing hemorrhagic pneumonitis, right lung.

CASE II. N. E., a thirty-seven year old housewife with chronic myelogenous leukemia, was admitted to the Clinical Center for the third time on April 25, 1956.

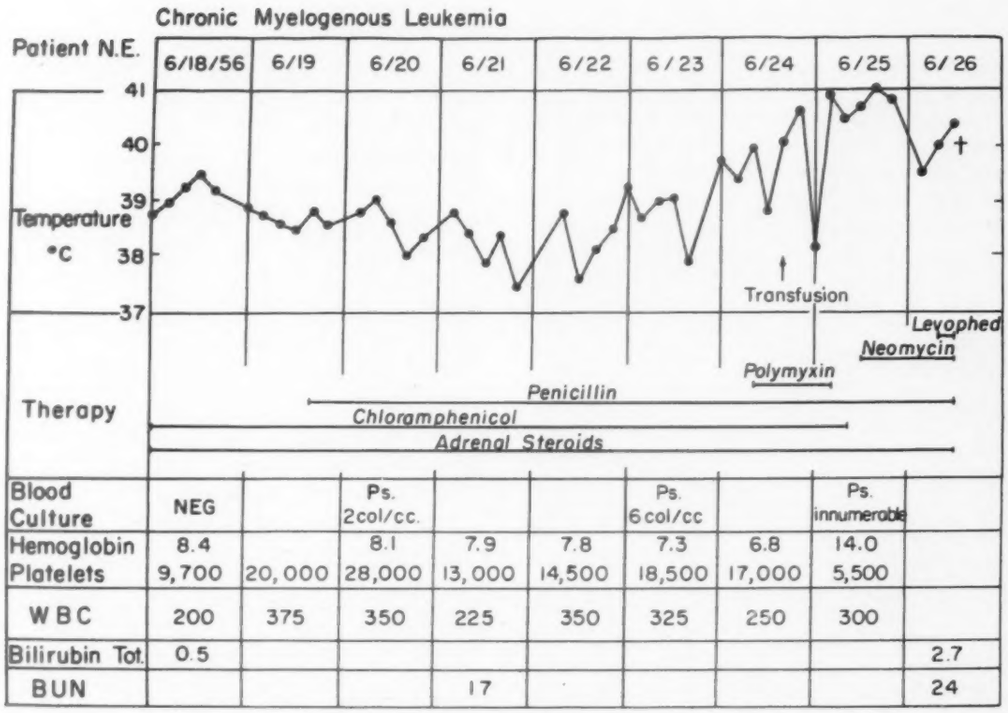
After twenty-one days 6-mercaptopurine was discontinued because of thrombocytopenia and oral ulcerations. Progressive suppurative gingivitis developed, which became necrotic. Prednisone was started at a dosage of 40 mg. daily and increased to 1,000 mg. daily but stopped after thirty-six hours because of mental depresson. By June 18 (Fig. 2) there was fever, marked oral pain, a gallop rhythm and progressive abdominal distention. Ps. aeruginosa was grown from cultures of the necrotic buccal mucosa and subsequently from the blood. The patient became disoriented and delirious. On June 25, the day before death, tender, red nodules (Janeway spots) were noted on the palms and soles. Her left knee became hot, tender and swollen. X-ray films showed pneumonia of the right upper lobe. Because stiff neck and bilateral Babinski responses were noted the spinal fluid was cultured and Ps. aeruginosa was isolated. Therapy during the last three days of life consisted of polymyxin-B, neomycin, penicillin and chloramphenicol. Terminally she became jaundiced and comatose, and died in shock.

At autopsy, microscopic examination of sections of sternum, vertebra, clavicle, rib and left femur revealed a sparsely cellular marrow populated by some reticulum cells, plasma cells, lymphocytes, and by greater numbers of atypical granulocytes. Similar granulocytes were seen in sections of the spleen.

Widespread septicemic lesions were present. The entire walls of some small arteries, veins and capillaries were intensely hematoxyphylic and contained numerous colonies of gram-negative bacteria. In none of the numerous extrapulmonary lesions was there a purulent inflammatory reaction. Several areas of confluent hemorrhagic consolidation were present in the lungs. The pneumonic areas of the right lung consisted of lobules filled with blood and fibrin; bacteria filled adjacent capillaries and were present in some alveolar spaces. In the vessels of the upper lobe of the left lung organisms having the morphologic appearances of aspergillus were seen.

Ps. aeruginosa was grown from turbid fluid aspirated from the left knee joint. Microscopic examination of the synovial membrane revealed bacterial colonies on its surface and in the walls of synovial vessels.

On the palms of each hand were about a dozen hemorrhagic lesions consisting of indurated centers of pinpoint size surrounded by erythematous halos.



Blood Culture	NEG		Ps. 2col/cc.			Ps. 6 col/cc		Ps. innumerable	
Hemoglobin	8.4		8.1	7.9	7.8	7.3	6.8	14.0	
Platelets	9,700	20,000	28,000	13,000	14,500	18,500	17,000	5,500	
WBC	200	375	350	225	350	325	250	300	
Bilirubin Tot.	0.5								2.7
BUN				17					24

FIG. 2. Case II. Pseudomonas septicemia developing on antibiotic therapy.

Microscopic examination revealed masses of bacteria and thrombotic material distending the vessels in the dermis. (Fig. 3.)

Gross examination of the brain and spinal cord revealed diffuse hemorrhage and fibrinous exudation on the parasagittal surfaces of the cerebral cortex. Microscopic examination of sections of the brain revealed diffuse bacterial vascular lesions.

The diagnoses at autopsy were: chronic myelocytic leukemia, fibrosis and osteosclerosis, bone marrow; septicemia (Ps. aeruginosa) with widespread bacteria-laden thrombi and hemorrhages, skin (including Janeway spots of palms), conjunctivas, peritoneum, pleura, lungs, kidneys, ureters, urinary bladder, spleen, adrenal glands, pituitary gland, left knee joint, lymph nodes, meninges, brain, and spinal cord; lobular pneumonia, upper lobe of right lung; mycotic pneumonia (Aspergillus), upper lobe of left lung; acute infectious arthritis, left knee (Ps. aeruginosa); chronic ulcerative gingivoglossopharyngitis and proctitis.

CASE III. A. G., a thirty-four year old white woman had been well until six years prior to admission to the Clinical Center when she was found to have chronic lymphocytic leukemia. For two years she had noted a chronic cough productive of foul, green sputum.

She was admitted on March 9, 1954, with persistent fever. Studies revealed bilateral bronchiectasis of the lower lobe. Ps. aeruginosa and Micrococcus pyogenes v. aureus persisted in the nose, pharynx and sputum in spite of antibiotic therapy. Fever continued. On May 20 a swelling on the right cheek adjacent to her nose appeared and this progressed to involve the right upper and lower eyelids. An x-ray film of the chest on June 2 showed pneumonitis in both lower lobes. The following day a red nodule, 0.5 cm. in diameter, was noted on the left anterior mid-thigh. Tetracycline and streptomycin therapy was started. On June 4, the day prior to death, Ps. aeruginosa was isolated in pure culture from the patient's blood. Numerous cutaneous nodules were noted all over the body, and

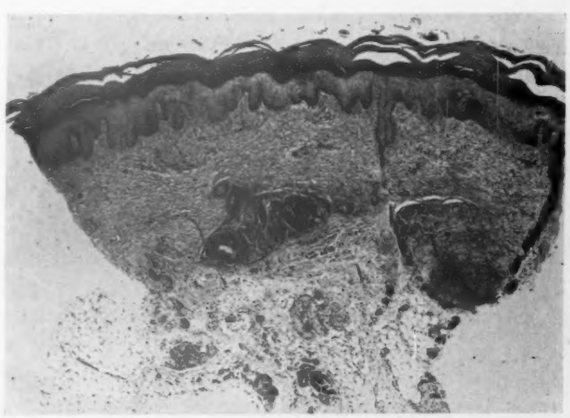


FIG. 3. Case II. Septic emboli, dermis, palmar skin. Hematoxylin-eosin stain.

an abscess developed at the tip of her left fourth finger. Terminally nuchal ridigity and a Babinski response developed; she became disoriented, semicomatose, and died in coma.

At autopsy, the lungs were heavy, inelastic, voluminous, and covered by shaggy pleural exudate. In all lobes there were areas of nodular induration which proved to be cylindrically ectatic bronchi. Numerous abscesses, measuring 3 cm. or less in diameter, were seen throughout the lungs. In the lower lobe of the right lung there was a pulmonary vessel which contained a thrombus and seemed to communicate with a small extravascular abscess. Other abscesses were discovered in the myocardium, liver, spleen, pancreas, duodenum, jejunum, thyroid gland and kidneys, all of which contained gram-negative rod shaped bacteria. Similar bacteria were seen in the meninges, ependyma and choroid plexus.

The diagnoses at autopsy were: chronic lymphocytic leukemia; cylindrical bronchiectasis, and lobular pneumonia with abscess formation, all lobes of the lungs; infected bronchiectasis, lower lobe of the left lung; infected thrombus pulmonary vein, lower lobe of the right lung; septicemia (Ps. aeruginosa) with multiple abscesses of heart, liver, spleen, pancreas, duodenum, jejunum, thyroid gland and kidneys; acute purulent leptomeningitis and ependymitis; and acute fibrinous pericarditis.

CLINICAL FEATURES

Between May 1954 and January 1957 twenty-two patients at the Clinical Center, National Institutes of Health, died of septicemia due to Ps. aeruginosa. One additional patient with a mixed septicemia (Ps. aeruginosa and Escherichia coli) which developed after manipulation of a ureteral catheter, survived. All but two of the twenty-three patients had malignant neoplastic disease. (Table 1.)

Of the twenty-three patients, thirteen had acute leukemia. The literature reveals only one or two detailed case reports of generalized pseudomonas infection occurring in patients with acute leukemia [*7,8*]. Our patients were usually but not invariably in a debilitated state when the infection occurred. In most cases antimicrobial therapy had previously been administered for the treatment of infection and adrenal steroids had been given for the control of rapidly progressive leukemia.

Essential features of the twenty-three cases are recorded in Table 1. The presumed portals of entry of Ps. aeruginosa were varied, but the most frequent sites were the skin and mucous membranes. In the twenty-two fatal cases the median duration of life following the first positive blood culture was 4.0 days. Twelve of the twenty-three patients (52 per cent) had jaundice concurrently with their septicemia. In six patients pseudomonas meningitis developed, and in two patients (N. E. and C. S.) septic arthritis developed. Nearly all the patients had marked abdominal distention. Following the onset of septicemia abnormal neurological manifestations in the form of apprehension, disorientation, tremors, convulsions and coma were observed in fifteen patients. Congestive heart failure was a prominent preterminal event.

Terminally, all twenty-two patients experienced a precipitous and profound fall in blood pressure which generally was unresponsive to the administration of whole blood. Vasopressor agents (usually levoarterenol) were transiently effective, but refractory shock inevitably ensued. The warm, flushed extremities and full, bounding pulse said to be characteristic of bacteremic shock from contaminated transfusions [*9*] were not observed.

Nine of twenty-three patients (39 per cent) had cutaneous lesions similar to those described previously in association with pseudomonas infections. These will be described under four separate categories.

First, and most striking, were lesions commonly termed ecthyma gangrenosa [*10*]. These were characteristically round, indurated, ulcerated areas with black, necrotic centers. (Fig. 4.) Some had rolled edges with a narrow erythematous zone surrounding the indurated central area. Inflammatory reaction and pus formation were minimal. These varied in size and occurred most frequently in the anogenital area. Except for the presence of bacteria, these lesions clinically and histologically resemble those of the Shwartzman reaction [*11*].

In the second category are the vesicular lesions [*12–14*] which tend to occur in clusters. (Fig. 5.) Small blebs or vesicles appeared on an erythematous base and contained a cloudy, opalescent fluid from which Ps. aeruginosa could be cultured. In contrast to the ecthymatous lesions, these were inflamed and painful. The vesicles eventually ruptured and then assumed either an ecthymatous appearance or healed completely.

A third type of lesion appeared as a flat and sharply demarcated cellulitis which would rapidly enlarge and become hemorrhagic and necrotic. (Fig. 6.) Such areas were usually not painful.

In the fourth category were small, pink, round



FIG. 4. Case B. H. Typical appearance of ecthyma gangrenosum.



FIG. 5. A cluster of vesicular lesions from which Ps. aeruginosa was obtained in pure culture. The surrounding areas of inflammation are best seen in color reproductions.

or oval maculopapular plaques or nodules, characteristically found on the trunk. These measured less than 2.0 cm. in greatest diameter, were symptom free and appeared prior to the obtaining of positive blood cultures. Lesions of similar description associated with generalized pseudomonas infection have been described [*13,15*].

In the course of pseudomonas septicemia, metastatic abscesses may appear in any part of the body. We have seen them develop rapidly in the extremities and finger tips (patients C. S. and C. B.).

Treatment. In each of the twenty-three patients therapy with antimicrobial drugs was begun at the time a presumptive diagnosis of septicemia was made but the nature of the organism was unknown. The short duration of life once Pseudomonas septicemia occurred precluded the institution of specific treatment in some cases. However, nine of the twenty-three patients were treated with polymyxin-B. In all but one of these nine patients, therapy was started within forty-eight hours of the positive blood culture. Polymyxin was administered intramuscularly in a dose of 3 mg. per kg., the total daily dosage not exceeding 0.2 gm. In eight of



FIG. 6. Shallow, sharply demarcated areas of gangrenous cellulitis due to Ps. aeruginosa. Surrounding areas with purpura and multiple petechiae are evident.

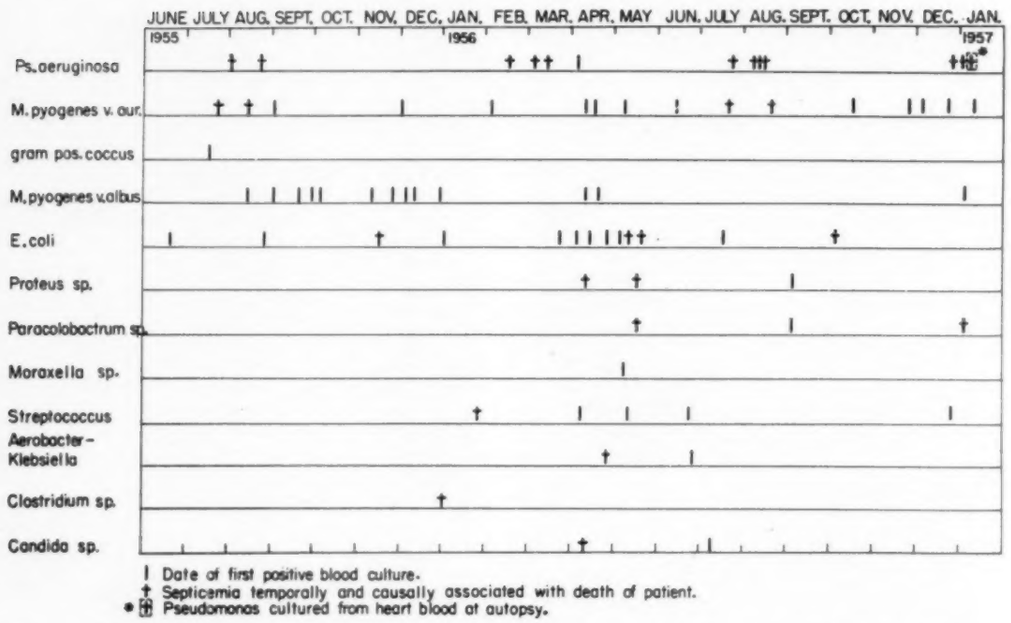


FIG. 7. The chronological pattern of septicemia episodes occurring on the acute leukemia service over a twenty-month period.

these nine patients polymyxin therapy was added to streptomycin and a tetracycline compound. Two patients received neomycin. All of the fourteen patients not treated with polymyxin received a tetracycline drug, chloramphenicol, streptomycin, neomycin, or combinations thereof.

Sensitivity studies by tube dilution technics were performed on organisms isolated from ten different patients. The bacteria isolated from the blood of nine of these patients were found to be sensitive to amounts of polymyxin (12 μg. or less) considered attainable in the serum on the dosage given.

In an additional eight cases sensitivity studies by disc technics were available. Six of eight organisms showed inhibition of growth in a zone surrounding the disc containing 30 μg. of polymyxin.

Pathology. Lesions containing gram-negative bacteria were most often seen in the lungs, skin and mouth. (Table 1.) The thyroid gland, kidneys, liver, lymph nodes, salivary glands, meninges, joints and intestinal tract were less frequently affected. These lesions consisted of a diffuse, acute, necrotizing vasculitis in which the walls of small arteries and veins were extensively invaded by pseudomonas. This process was associated with extravascular hemorrhage and intravascular thrombosis. There was edema and bland necrosis of the area supplied by the affected vessels. Progressive changes in the necrotic parts resulted in septic necrosis, or in hemorrhagic, gangrenous ulcers. The organisms gradually disseminated by way of the vessels at the periphery of the lesion, which gradually enlarged and varied in color from red to green, dark brown and black. The walls of vessels affected by Ps. aeruginosa appeared thickened, blurred and blue because of the large clumps of bacteria and the profound degenerative changes. The bacteria were frequently localized in the vessel wall, which is characteristic of pseudomonas infections [*16*] and predisposes to septicemia.

Epidemiology. A group of patients, all with acute leukemia, were selected for epidemiologic study as they had been treated on one nursing unit, exposed to the same physicians, nurses and attendants, and had been fed from the same kitchen. Episodes of septicemia of whatever cause during a twenty-month period are illustrated in Figure 7. The date on which the first positive blood culture was obtained is indicated.

All episodes were separated by clinical evidence of cure as well as by negative blood cultures. In contrast to other septicemias, those due to Ps. aeruginosa occurred in small groups. Episodes of septicemia temporally and causally related to the patient's death were located predominately in the pseudomonas series. The

TABLE II
CAUSATIVE AGENTS OF SEPTICEMIA ON THE ACUTE LEUKEMIA SERVICE OVER A TWO-YEAR PERIOD

Agent	No of Episodes	No of Patients*
M. pyogenes v. aureus	18	15
Ps. aeruginosa	13	13
M. pyogenes v. albus	13	9
E. coli	13	7
Streptococcus	5	5
Proteus sp.	3	3
Paracolobactrum sp.	3	3
Aerobacter klebsiella	2	2
Clostridium sp.	2	2
Candida sp.	2	2
Moraxella sp.	1	1
Gram-positive coccus†	1	1
Total	76	..

* Several patients had episodes with more than one organism.

† Not further identified.

TABLE III
COMPARISON OF SEPTICEMIAS DUE TO GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS AS RELATED TO PRIOR ANTIMICROBIAL THERAPY

Etiologic Agent	No. of Septicemias	Antimicrobial Therapy*		
		None	Narrow Spectrum†	Broad Spectrum‡
Gram-positive organisms:				
M. pyogenes v. aureus	18	10	2	6
M. pyogenes v. albus	13	8	0	5
Streptococci	5	2	1	2
Gram-positive coccus	1	1	0	0
Clostridium sp.	2	2	0	0
Total	39	23	3	13
Gram-negative organisms:				
E. coli	13	5	1	7
Ps. aeruginosa	13	2	1	10
Paracolobactrum sp.	3	1	0	2
Proteus sp.	3	1	0	2
Moraxella sp.	1	1	0	0
A. klebsiella	2	1	0	1
Total	35	11	2	22
Candida sp.	2	0	0	2

* Includes only antimicrobial therapy continued from more than five days prior to septicemia to within forty-eight hours of septicemia.

† Penicillin, streptomycin, erythromycin, penicillin and erythromycin, and Gantrisin.®

‡ Penicillin and streptomycin, all tetracyclines, chloramphenicol, neomycin, and combinations thereof.

TABLE IV
RELATIONSHIP OF ADRENAL STEROID AND ACTH THERAPY TO SEPTICEMIA

Causative Organism	No. of Septicemias	No. of Patients on Steroid Therapy*	No. of Patients Not on Steroid Therapy
Ps. aeruginosa	13	8	5
E. coli	13	8	5
M. pyogenes v. aureus	18	9	9
M. pyogenes v. albus	13	5	8

* Does not include patients in whom therapy with adrenal steroid or ACTH was started within the forty-eight hours preceding the first positive blood culture.

relative incidence of septicemias from all causes in eighty-seven consecutive patients with acute leukemia over a two-year period is shown in Table II.

Superinfection. Data relating to the influence of prior antimicrobial therapy on the development of septicemia are shown in Table III. All febrile patients were studied and their episodes of fever investigated and classified according to a predetermined protocol [*6*].

Of the thirteen pseudomonas septicemias, ten (seventy-seven per cent) occurred in patients receiving broad-spectrum antimicrobial therapy whereas the respective figure for other gram-negative septicemias was only twelve of twenty-two (55 per cent), and for gram-positive infections only thirteen of thirty-nine (33 per cent). The data, therefore, add to the evidence [*2,3,17–20*] that Ps. aeruginosa is a common superinfecting organism.

Adrenal Steroids. Seventy-six consecutive episodes of septicemia in patients with acute leukemia were analyzed with respect to the temporal relationship of adrenal steroid therapy to the development of septicemia. Patient-days on adrenal steroid therapy could not be compared with patient-days not on steroid therapy because, in general, patients in the former group had more advanced disease. However, it was possible to evaluate the relative incidence of septicemias due to the various causative organisms in relation to administered adrenal steroids. The results are shown in Table IV.

The data do not permit conclusions regarding the role of adrenal steroids in the incidence of septicemias. Although gram-negative bacterial septicemias were somewhat more likely to occur than septicemias due to gram-positive bacteria in patients receiving adrenal steroids, the difference was not significant (p greater than .05).

Antimetabolites. With respect to the administration of antimetabolites, a valid comparison

TABLE V
RELATIONSHIP OF ANTIMETABOLITE THERAPY TO DEATH DUE TO SEPTICEMIA IN PATIENTS WITH ACUTE LEUKEMIA

Cause of Death	No. of Patients	No. of Patients on Antimetabolites*	No. of Patients on Antimetabolites with Toxicity†
Septicemia	28	13	6
Ps. aeruginosa	13	9	5
Other bacteria	15	4	1
Other than septicemia	34	14	7
Total	62	27	13

* Methotrexate or 6-mercaptopurine administered within ten days of death.

† Toxicity evaluated on the basis of toxic oral ulcerations, hypoplastic bone marrow, and gastrointestinal symptoms not attributable to other causes.

can be drawn between deaths due to pseudomonas septicemia and death associated with other bacterial septicemias. The data in Table v indicate that of sixty-two consecutive deaths in patients with acute leukemias, twenty-eight (45 per cent) were associated with septicemia. Thirteen, or nearly half of these fatal septicemias, were due to Ps. aeruginosa. It is apparent that, in the presence of antimetabolites, deaths from pseudomonas septicemia were relatively more frequent than were deaths from other bacterial septicemias. This difference is even more striking for those deaths due to infection, associated with antimetabolite toxicity. Although the number of patients involved is small, the data suggest that the administration of antimetabolites does in some way increase the susceptibility of patients to pseudomonas septicemia.

*Gamma Globulin.** No consistent quantitative abnormality has been found to differentiate the serum gamma globulin levels of patients with acute leukemia from those of normal persons in other studies [*21–22*]. Patients in whom infection with Ps. aeruginosa developed showed no consistent quantitative change of serum gamma globulin values. Most levels started and remained within the normal limits of variation.

* The electrophoretic studies of the serum proteins were performed in the laboratory of Dr. John Fahey of the National Cancer Institute.

Recently published studies on mice indicate that human serum gamma globulin will protect to a certain extent against experimental pseudomonas infections [*23*]. In view of this increasing frequency of pseudomonas infections in selected groups of patients it would be important to know if man could be similarly protected by gamma globulin administration.

COMMENTS

In twenty-three patients with pseudomonas septicemia, certain clinical features occurred repeatedly. In 52 per cent jaundice developed and 65 per cent had neurological disorders. Neurotoxicity with pseudomonas infection has been observed in animals [*24*] and possibly in man [*25*]. Stevens and co-workers [*26*] described an eighteen year old boy who died sixty-six hours following transfusion of blood contaminated with pseudomonas specie. The clinical phenomena observed in this patient were seen in many of our patients. Stevens suggested the possibility that a "toxin" played a significant role in the patient's symptoms and death as antibiotics were effective in sterilizing the patient's blood. In three of our patients antibiotics were effective in sterilizing the blood but clinical improvement did not occur.

Rolly [*27*], among other early writers, stressed the presence of a hemorrhagic diathesis and abnormal coagulability of the blood. Numerous reports [*28–30*] have stressed the fact that severe pseudomonas infections may produce granulocytopenia. Experimental work has shown that Ps. aeruginosa or its toxin can induce granulocytopenia in animals [*31–34*] and injections of endotoxin from gram-negative bacteria can produce a similar phenomenon in man [*35*].

Although polymyxin-B is generally accepted as the therapy of choice, analysis of sensitivity studies performed on the bacterial isolates from these patients showed that, on an *in vitro* basis, neomycin was superior to polymyxin-B. The small number of patients treated with neomycin, and the almost invariably fatal outcome prevented satisfactory evaluation of this drug *in vivo*. Short patient-survival times precluded extended specific therapy. In our series, even the best available antimicrobial agents did not affect the rapid and almost uniformly fatal outcome.

On the acute leukemia service pseudomonas infections frequently occurred in small "epidemics." The factors responsible are as yet unknown but are under investigation. Epidemics

due to Ps. aeruginosa are rare but have been described with relation to infantile diarrhea [*36–38*], omphalitis [*39*] and gastroenteritis [*40*]. An epidemic of pseudomonas meningitis presumably resulting from contamination of medicines has occurred [*41*].

Many factors contribute to lowered host resistance in patients with acute leukemia. Among these are granulocytopenia, mucosal bleeding, leukemic infiltrates of the gums, oral cavity and intestinal tract, and malnutrition. Antibody response and altered phagocytic properties of abnormal leukocytes in these patients have been investigated in this connection [*6*].

Adrenal steroids or adrenocorticotrophic hormone may favorably affect the course of severe infections [*42–44*]. Conversely, there is evidence, particularly in experimental infections [*45–47*] but also in certain infections in humans [*48–49*], that these hormones may exert an adverse effect. Millican [*47*] found that cortisone increased the susceptibility of mice to infections with Ps. aeruginosa.

Infections, particularly those due to gram-negative bacteria, frequently occur in patients receiving adrenal steroids. Patients in whom pseudomonas septicemia developed in the absence of adrenal steroids received no apparent benefit from their subsequent administration.

The toxic manifestations of both total body radiation and antimetabolite compounds have much in common. Recently reported experiments have shown that mice subjected to radiation frequently died of pseudomonas septicemia [*50*]. Our data would suggest that patients treated with antimetabolites especially those treated to toxicity, are more likely to acquire pseudomonas septicemia, a development possibly related to adverse effects of antimetabolites on host resistance. In particular, the possibility that bacterial seeding may originate in the areas of damaged bowel mucosa must be considered.

SUMMARY AND CONCLUSIONS

1. Twenty-three cases of pseudomonas septicemia occurring at the Clinical Center of the National Institutes of Health from 1954 to 1957 have been investigated.

2. Common clinical manifestations of pseudomonas septicemia have been characteristic cutaneous lesions, progressive jaundice, neurological abnormalities, arrhythmia, ileus and the sudden development of hypotension.

3. Twenty-two of the twenty-three cases were fatal. The median duration of life following the first positive blood culture was 4.0 days.

4. The characteristic gross and microscopic morphologic changes of primary and secondary pseudomonas lesions are described and illustrated. The affinity of this microorganism for the walls of small vessels is stressed.

5. Thirteen patients with acute leukemia were selected as a group for the analysis of epidemiology and host resistance. Ps. aeruginosa has been the second most frequent cause of septicemia and the most frequent bacterial cause of death on the leukemia service.

6. Analyzed chronologically, cases of pseudomonas septicemia on the acute leukemia service were noted to occur in groups. This was in contrast to the random distribution of other bacterial septicemias occurring on that service.

7. Gram-negative septicemias occurred more frequently than septicemias due to gram-positive bacteria in patients receiving adrenal steroid therapy.

8. Pseudomonas septicemia frequently occurred as a superinfection. Seventy-seven per cent occurred despite broad-spectrum antimicrobial therapy, whereas only 33 per cent of septicemias due to M. pyogenes v. aureus occurred under these conditions.

9. There is suggestive evidence that antimetabolite administration may in some way predispose to the development of pseudomonas septicemia.

Acknowledgment: The authors wish to thank Dr. Charles G. Zubrod for his suggestions and criticisms in the preparation of this work.

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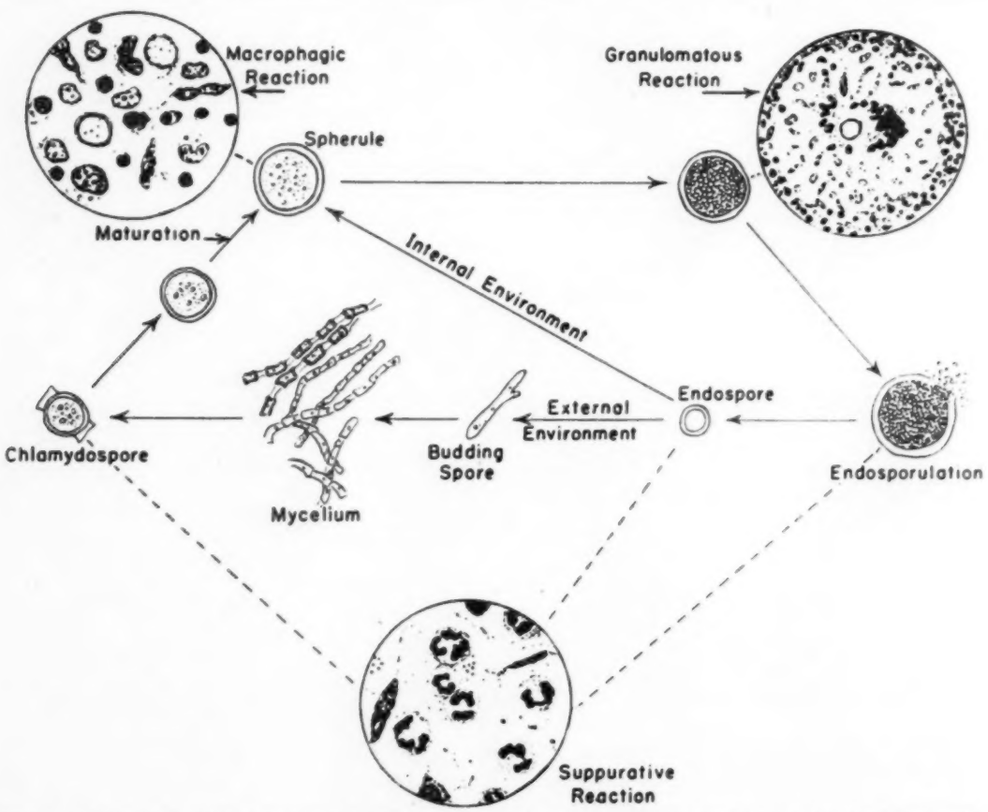
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Coccidioidal Pulmonary Cavitation*

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COCCIDIOIDOMYCOSIS is a fungus disease endemic to large areas of the southwestern United States. With the exposure of many people during military service and the recent increase in vacation travel and transcontinental visits, patients with coccidioidomycosis are being seen everywhere and the disease is of importance to all physicians. Coccidioidomycosis has been well summarized [*1–4*] and the general subject will be reviewed only briefly [*5*].

Chlamydospores or arthrospores, the infectious "vegetative" form of Coccidioides immitis, enter the body through the respiratory tract, usually through the air but occasionally on clothing or other dust-contaminated objects. The arthrospores develop into doubly refractive spherules which reproduce by endosporulation. (Fig. 1.) Infection is more common during the dry, dusty season (July through October). Endemic areas include California, southern



LIFE CYCLE OF COCCIDIOIDES IMMITIS AND RELATED HISTOLOGICAL RESPONSE

FIG. 1. Life cycle of C. immitis and related histologic response. (From: FORBUS, W. D. and BESTEBREURTJE, A. M. Coccidioidomycosis; study of 95 cases of disseminated type with special reference to pathogenesis of disease. *Mil. Surgeon*, 99: 654, 1946.)

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FIG. 2. Known coccidioidal endemic areas in the United States. (From: SMITH, C. E. Diagnosis of pulmonary coccidioidal infections. *California Med.*, 75: 387, 1951.)

and central Arizona, southern New Mexico, and western Texas. (Fig. 2.) The incubation period is one to three weeks, usually ten to sixteen days. The disease is not infectious.

Primary pulmonary infection is most commonly asymptomatic, localized and self-limited. The usual course is uncomplicated healing of the primary lesion, occasionally with fibrosis and calcification. The only evidence of infection may be a positive coccidioidin skin test. This becomes positive in man from ten to forty-five days after exposure, usually during the second or third week following inhalation of arthrospores. However, up to two-thirds of the patients with disseminated coccidioidomycosis fail to react to 1:100 dilutions of coccidioidin. Unless dissemination is suspected or the cause of a pulmonary cavity is unknown, a negative coccidioidin skin test should screen out the serologic test, since humoral antibodies are not present prior to the development of skin sensitivity to coccidioidin. With very mild infections the serology may never become positive. Generally precipitins develop earlier and vanish sooner than do the complement fixing antibodies. The latter have important prognostic value for only rarely are they negative in disseminated disease.

Initial primary infection is nearly always pulmonary and well localized. At least 60 per cent of the patients are asymptomatic and the infection is recognized only by the development of a positive coccidioidin skin test. Some patients have symptoms of upper respiratory disease or "influenza." The fungus may be found in the sputum and the coccidioidin skin test will usually be positive. A chest roentgenogram may reveal a bronchopneumonic lesion, enlarged hilar lymph nodes or occasionally pleural effusion. About 5 per cent of patients have erythema nodosum or erythema multiforme.

The diagnosis of coccidioidomycosis can be established definitely by isolating the fungus on culture. The presence of coccidioidal antibodies in the blood serum is also diagnostic. A positive coccidioidin skin test indicates either present or past infection, and alone is not diagnostic of active disease. However, conversion from a negative to a positive skin test indicates recent coccidioidal infection. Symptoms frequently noted include fever, chest pain, cough, malaise, anorexia and pleural pain. (Fig. 3.) The incidence of hemoptysis, usually minimal, varies from 3 to 28 per cent in different series.

Four types of roentgenographic findings have been noted: (1) by far the most common, a non-specific bronchopneumonic density varying

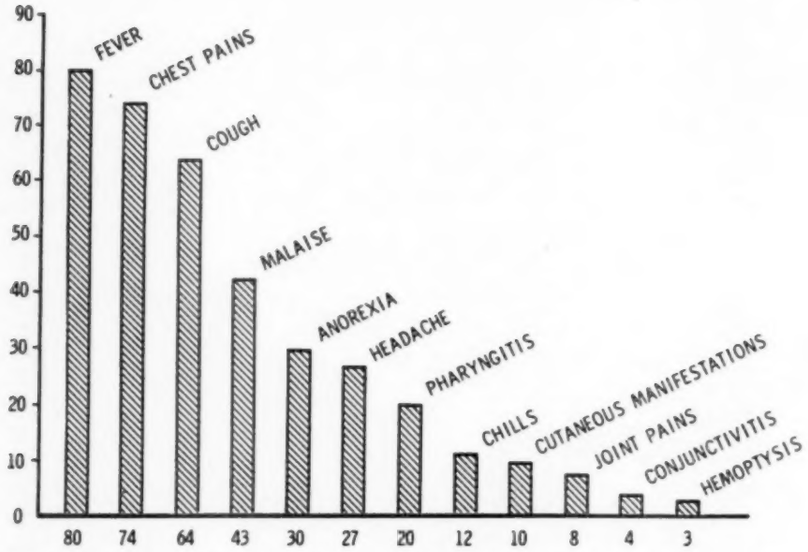


FIG. 3. Frequency of symptoms in 100 patients hospitalized for pulmonary coccidioidomycosis. (Modified from WILLETT, F. M. and WEISS, A. [*8*].)

in size but usually less than one-third or one-fourth of a lung field; (2) cavities, often thin-walled, usually develop within a broncho-pneumonic density so that the thickness of the cavity "wall" depends on the amount of surrounding pneumonia, at least early in the disease; (3) hilar adenopathy, which is very suggestive in a patient who has been in an endemic area; and (4) a small dense nodule, coccidioma, which represents the healed fibrotic residuum.

Disseminated coccidioidomycosis is an unusual complication, occurring once in about 750 cases. This usually occurs as a direct extension or continuation of the primary infection and is more common in darker skinned persons, such as Mexicans, Negroes or Filipinos, in whom dissemination has been noted as often as once in forty cases. The mortality rate in disseminated cases is about 50 per cent.

Treatment of primary coccidioidomycosis varies from none to mild symptomatic therapy. Bedrest is indicated during the febrile period. With dissemination, treatment is unfortunately ineffective at the present time. Many drugs have been tried but to date none has been found effective. Amphotericin B is being used currently but this drug appears to be of doubtful value. The Veterans Administration Cooperative Study of Coccidioidomycosis will undoubtedly have definite information on this point in about a year since patients with disseminated coccidioidomycosis in this study are being treated with intravenous amphotericin B.

COCCIDIOIDAL CAVITATION

The article by Smith, Beard and Saito in 1948 [*6*] is a classic and thoroughly reviews this entity. These workers studied 274 patients with coccidioidal pulmonary cavities. They emphasize that in patients with cavitation the disease rarely disseminates and that these cavities are relatively benign. "The risk of dissemination being negligible and possibility of contagion very remote, drastic intervention should be reserved for specific indications" [*6*]. The present report is based on seventy-seven cases of coccidioidal pulmonary cavities collected over a twelve-year period.* This group coincided, in general, with the population of veterans of World War II. There were seventy-six males and one female. The median age was twenty-five years (range, eighteen to fifty-seven years). Ninety per cent were under forty years of age. (Table I.) There were sixty-nine white patients (including nine Latin Americans) and eight Negro patients. It is clear that the low percentage of non-Caucasians is quite different from a series of patients with disseminated coccidioidomycosis.

* Included in this study are twenty patients from the Veterans Administration-Armed Forces Cooperative Study of Coccidioidomycosis.

TABLE I
AGE OF PATIENT WHEN FIRST SEEN

Age (yr.)	No. of Patients	
Under 20	7	90%
21–30	43	
31–40	19	
41–50	7	
51 plus	1	

Incidence. Coccidioidal pulmonary cavitation occurs in about 2 to 3 per cent of those cases of primary infection which are sufficiently severe to require medical attention. The exact incidence is most difficult to determine since only about 25 to 40 per cent of patients with infections will seek medical attention. In Smith's large series of 753 cases, cavities were detected in 1.7 per cent of patients [*6*]. Other reported frequencies of cavitation in hospitalized patients are 6 to 8 per cent [*7*], 6 per cent [*8*], 4 per cent [*9*] and "perhaps 0.5 to 3 per cent" [*3*]. Birsner [*10*] reviewed 500 cases of pulmonary coccidioidomycosis in an endemic area and found sixty-one patients with cavitation.

Symptoms. Smith et al. [*6*] found that 58 per cent of cases of coccidioidal pulmonary cavitation in the military services were discovered on routine chest films. Among civilians, 24 per cent were detected in asymptomatic patients. This difference is readily explained by the greater frequency of routine chest x-ray films in military service. In our series of seventy-seven cases, 58 per cent were essentially asymptomatic and were detected on routine chest roentgenograms, 26 per cent were x-rayed because of hemoptysis, 6 per cent because of chest pain and 10 per cent because of acute respiratory symptoms. As noted in Table II, these figures for a veteran population are almost exactly similar to Smith's military group of 153 cavities. The asymptomatic nature of most coccidioidal cavities is apparent. Only twenty patients (26 per cent) of the present series gave any history of bleeding, and in most cases (thirteen of twenty patients) there had been only minimal blood streaking or a small hemoptysis. Cavitation occurs at the site of the original coccidioidal pneumonia. Generally there are no signs or symptoms during the process of cavitation in hospitalized patients [*3*].

TABLE II
REASON FOR CHEST X-RAY

	77 Veterans (%)	153 Military Personnel (Smith et al. [*6*]) (%)
Routine x-ray	58	58
Symptomatic	42	42
Acute respiratory symptoms	10	21
Bleeding	26	15
Chest pain	6	6

TABLE III
NUMBER AND SIDE OF CAVITIES

Data	Per cent
Number:	
Single	86
Multiple	14
Side:	
Right	58
Left	42
(bilateral in 3 patients)	

Number and Side of Cavities. Sixty-six patients (86 per cent) had single cavities and eleven (14 per cent) had multiple cavities. In Smith's group, 90 per cent had single cavities, the remainder being described as multiple or multilocular. Fifty-eight per cent of the cavities were on the right side and 42 per cent were on the left. There were bilateral cavities in three patients. In Smith's series, 55 per cent of cavities were in the right lung and 45 per cent were in the left lung. (Table III.)

Coccidioidin Skin Tests. A Berkefeld filtrate of a culture of multiple strains of C. immitis is used in a 1:100 dilution. Sensitization does not occur with repeated skin testing. A 1:1000 dilution is used for patients with erythema nodosum to avoid exacerbation of these skin lesions. To avoid non-specific reactions we do not use the 1:10 dilution. The use of coccidioidin has been very well summarized [*3,11*].

Of seventy-three patients with recorded skin tests, forty-two (57 per cent) were positive. In most cases the skin test was made only once, but in many cases skin tests were repeated on numerous occasions. In Smith's series, 90 per

TABLE IV
LABORATORY TESTS

Test	Per cent Positive
Coccidioidin skin test:	
Smith's series	90
Present series	57
Complement fixation test:	
Smith's series	74
Present series	64

cent of the patients with coccidioidal pulmonary cavitation had positive reactions to the 1:100 dilution. Dr. Smith uses his own antigen and it has been the experience of several observers that this material is more sensitive than the coccidioidin available commercially. That 43 per cent of the patients of this group of coccidioidal cavities had negative coccidioidin skin tests is rather disturbing and emphasizes the need for repeated skin tests, sputum studies for fungi and coccidioidal serologic studies whenever a pulmonary cavity is suspected of being coccidioidal in origin. (Table IV.)

Coccidioidal Serology. Smith and co-workers [*12*] have reviewed 39,500 serologic tests in coccidioidomycosis. Of 107 patients with pulmonary cavitation and positive sputums for C. immitis, 62 per cent had positive complement fixation antibodies and 12 per cent had equivocal reactions. Of fifty-seven patients with a reported coccidioidal complement fixation in the present series, thirty-seven (64 per cent) were positive, varying from equivocal (very slightly positive 1:1 or partial 1:2 reactions) to definitely positive reactions. These serological tests were performed in various laboratories including the University of California at Berkeley, Fort Miley Veterans Administration Hospital, San Francisco, and Walter Reed Army Medical Center, Washington, D. C. A comparison of complement fixation tests for coccidioidomycosis has been reported [*13*].

Therapy. Treatment of these seventy-seven patients varied greatly with different physicians. This provided an opportunity for comparing modes of therapy since a patient with an essentially asymptomatic coccidioidal pulmonary cavity would receive reassurance and conservative treatment from one physician and would have resectional surgery advised by another.

Non-surgical group: Cavity closure: There were thirty-six cases (46 per cent of the total group) treated non-surgically. Information about the status of the pulmonary cavity was available in twenty-nine patients. Of these, fifteen had open cavities when last observed, although almost all were asymptomatic and working; this included one patient whose cavity was known to be present for at least eight years, one for four years, and five for three years. The median duration of follow-up for this group was two years. In fourteen patients of this group of twenty-nine with adequate follow-up the cavities closed spontaneously. However, the date of closure was clear in only nine cases. Although one cavity closed after seventeen years and another after nine years, most cavities closed within three years and many within the first year of development. The median time for cavity closure was two years.

Symptoms: It is of interest to note that twenty-eight patients were asymptomatic and only eight had a history of bleeding. Seven of these eight patients had open cavities; three had 1 plus hemoptysis (unusual, small hemoptyses or blood streaking) and four had 2 plus hemoptysis (intermittent hemoptyses and/or bleeding of fair amount). In one additional patient with 2 plus hemoptysis the cavity closed spontaneously. No new cavities developed in any of the thirty-six patients treated non-surgically. (Table V.)

Surgical group: Forty-one patients (54 per cent of the group of seventy-seven pulmonary-

TABLE V
RESULTS OF NON-SURGICAL THERAPY (THIRTY-SIX PATIENTS, 46 PER CENT)

	No. of Patients
Status of pulmonary cavity in 29 patients followed up:	
Remained open (follow-up, to 8 yr.; median follow-up, 2 yr.)	15
Closed spontaneously (median follow-up, 2 yr.)	14
Symptoms:	
None	28 (77%)
Bleeding	8 (23%)
1 plus	3
2 plus	5
New cavities	0

TABLE VI
RESULTS OF RESECTIONAL THERAPY (FORTY-ONE PATIENTS, 54 PER CENT)

	No. of Patients
Symptoms:	
None	29 (71%)
Bleeding	12 (29%)
1 plus	10
2 plus	2
New cavities	8 (20%)

TABLE VII
INDICATIONS FOR SURGERY

	No. of Patients
Mistaken diagnosis	15
Thought to be tuberculosis	9
"For diagnosis"	5
Thought to be a cyst	1
Cavity on x-ray (asymptomatic)	12
History of bleeding	12
Enlarging peripheral cavity	2

cavitary patients) underwent resectional surgery. These patients were treated at various hospitals by various surgeons, and therefore represent a cross section of surgical management.

Symptoms: Twenty-nine patients were asymptomatic. Of twelve patients giving a history of hemoptysis, in ten it was mild (1 plus) and in two moderately severe or recurrent (2 plus). No patients had severe recurrent bleeding. (Table VI.)

Indications for surgery: These were: mistaken diagnosis, fifteen patients; presence of cavity on x-ray, twelve patients; history of bleeding, twelve patients; enlarging peripheral cavity, two patients. (Table VII.) It is of interest to note that in three patients who underwent resection because of "history of bleeding," the bleeding had occurred one and a half, two and four years before surgical resection, respectively.

Surgical complications: Twenty-seven patients had an essentially uneventful postoperative course. In twelve patients (29 per cent of those having resection) bronchopleural fistulas with empyema developed. Twenty additional surgical procedures were required including ten thoracotomies, eight thoracoplasties and two resections. (Table VIII.)

TABLE VIII
SURGICAL COMPLICATIONS

	No. of Patients	Per cent of 41 Resections
None	27	67
Complications	14	33
Bronchopleural fistula and empyema	12	29
Additional surgery required:		
Thoracotomy	10 procedures	..
Thoracoplasty	8 procedures	..
Lobectomy	2 procedures	..

TABLE IX
POSTOPERATIVE STATUS

	No. of Patients	Per cent
Well	20	63
Limited activity	4	12
Disabled (all with bronchopleural fistula)	8	25
Unknown	9	..

Coccidioidal complications: In eight patients (20 per cent) new cavities developed in lung tissue remaining after surgery. Of the nine patients with a history of recent preoperative bleeding (omitting the three patients who had bled one and a half, two and four years before surgery), four continued to bleed postoperatively. In two patients who had no presurgical bleeding blood streaking developed postoperatively.

Postoperative status: Twenty patients were well and working. Four patients were on limited activity because of chest pain or dyspnea. Eight patients were disabled, all with bronchopleural fistulas and unexpanded lungs. Three of these patients have been hospitalized continuously for more than two years. Nine additional patients were reviewed either too soon after surgery or were lost to follow-up. (Table IX.)

COMMENTS

As Moore et al. [*14*] have indicated, "There are many opinions as to the method of treatment of pulmonary cavitation in coccidioido-

mycosis. In some instances the patients have continued to work and the cavities have closed without any treatment." Forsee and Perkins [*15*] reported fifty patients (including thirty with pulmonary cavities) treated with surgical resection. Five patients had postoperative complications, including contralateral spread in one patient, recurrent cavitation in two patients and bronchopleural fistulas in two patients. Other writers note that resectional surgery is required only rarely. Berke and associates [*16*] have stated, "Nonintervention, therefore, should be the keynote of the therapy of these residual lung lesions. With only an occasional exception the condition is benign and the patient has few, if any, symptoms. Medicinal treatment is of no specific value . . . We wish to emphasize that pneumothorax, or other surgical intervention, is not indicated, except in the infrequent case where there is significant hemorrhage from a cavity." Smith and his co-workers [*6*] did not see a single case of dissemination in their series of 274 coccidioidal pulmonary cavities, and note that "the prognosis is favorable . . . Conservatism is desirable, recalling that there is no bronchogenic spread from cavities, nor are such patients contagious." Resection of a cavity is not always curative and has been followed by the appearance of new cavities in remaining lung tissue [*2,3,14,15,17,18*]. Indeed, in 20 per cent of the present series of patients undergoing surgical resection, cavities developed in the remaining lung tissue postoperatively. Dissemination with or after coccidioidal pulmonary cavitation is very rare [*1–3,5,6*]. Timmes and Baum [*19*] note, "Since the localized form of pulmonary coccidioidomycosis is generally self-limited and since uncomplicated cavitary disease apparently causes no harm, resection appears to be indicated only in cases where coccidioma could be confused with carcinoma, or in complications of coccidioidal cavitation . . . Though the present series of cases is far too small to draw any definite conclusion, there is a suggestion that resectional surgery in coccidioidomycosis is more frequently complicated by postoperative persistent air leak and pleural disease than is similar surgery in other conditions."

Winn [*20*] recommends surgery for very large cavities (over 4 cm. in diameter) and in those patients with recurrent severe hemoptysis, and states " . . . that thoracic surgeons may be somewhat overdoing resections for this disease. Complications of the surgical procedures used in eradicating coccidioidal disease foci from the lungs are not infrequent and are occasionally severe." Smith [*6*] has stated, "Unless there is a definite indication . . . , the patient may well be left alone with his cavity. Unfortunately, a mistaken analogy with tuberculosis is apt to drive us into taking drastic steps which the health of the patient does not warrant."

Comparing the non-surgical and resection groups of the present series, one must conclude that except for large, peripheral or enlarging [*21*] coccidioidal pulmonary cavities, the non-surgical group is bound to do very well. These patients are either asymptomatic or have learned not to worry about occasional blood streaking, and have been able to do work and hold a job. There were no complications, no new cavities and no deaths.

In the surgical group, bronchopleural fistulas and empyema developed in 29 per cent of the patients with resections. There were twenty additional surgical procedures required, occasionally several in the same patient, including ten thoracotomies, eight thoracoplasties and two lobectomies. In 20 per cent of the operated patients new cavities developed postsurgically. It is of interest that in seven of these eight patients the new cavity was treated conservatively. In the eighth patient further surgery included lucite plombage, thoracoplasty and further resection. Eight of the surgical patients were disabled with bronchopleural fistulas. There were no deaths in the present series.

SUMMARY

1. Seventy-seven cases of coccidioidal pulmonary cavitation have been summarized.

2. Cavitation is found in about 1 to 3 per cent of hospitalized patients with coccidioidomycosis, or about 0.1 per cent of all patients with this disease.

3. Fifty-eight per cent of the group were asymptomatic and the condition was detected on routine chest x-ray films.

4. Eighty-six per cent of patients had a single cavity and 14 per cent had multiple cavities. Fifty-eight per cent were in the right lung, 42 per cent in the left lung, and three patients had bilateral cavities.

5. Only 57 per cent of the patients in the present series had positive coccidioidin skin tests. Sixty-four per cent had positive complement fixation antibodies in varying degrees.

6. Non-surgical and surgical management of coccidioidal pulmonary cavities has been compared. In the former group, half of the cavities closed spontaneously. Most patients were asymptomatic but 22 per cent of this group had bleeding, usually slight, at some time. No new cavities developed.

7. In the surgical group most were asymptomatic, although 30 per cent gave a history of bleeding. There were no deaths but in 29 per cent of the patients with resection, bronchopleural fistulas with empyema developed and twenty additional surgical procedures were required. Furthermore, new cavities appeared postoperatively in 20 per cent of the patients who underwent resection.

8. On the basis of the aforementioned data, a conservative, non-surgical regimen appears most desirable for coccidioidal pulmonary cavity unless (1) the cavity is over 4 cm. in diameter, (2) the cavity is enlarging significantly or (3) there are recurrent, severe hemoptyses.

Acknowledgment: Grateful acknowledgment is made to Mr. Timothy Dodge of the Medical Illustration Department of the hospital for the illustrations, and to Miss Virginia Burger for clerical assistance.

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Jaundice Associated with the Administration of Iproniazid*

Report of Nine Cases

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IN 1952, reports of the antituberculous activity of iproniazid (1-isonicotinyl-2-isopropyl hydrazine, Marsilid®) in animals [*1–3*] were soon followed by preliminary reports of its therapeutic efficacy in human tuberculosis [*4–6*]. Frequent side effects were noted [*7–9*] which were primarily related to the nervous system. Studies for potential hepatic toxicity were made [*6,8,10–12*] but jaundice occurring during therapy was attributed to other factors or was not further clarified [*13–16*].

Isoniazid (isonicotinic acid hydrazide), a chemically related compound, became available at about the same time as iproniazid. Animal experiments [*17–19*] were not conclusive regarding comparative nervous system toxicity but studies in patients with tuberculosis [*8,20*] showed a significantly greater incidence of both minor and major undesirable side reactions with iproniazid than with isoniazid therapy. Therefore isoniazid almost completely replaced iproniazid in the treatment of tuberculosis [*13,14,21*]. Since isoniazid was available when iproniazid was still being used only for experimental purposes, the latter was never widely employed in the treatment of tuberculosis and after the preliminary studies was used for this purpose in comparatively few instances [*22*].

Attempts were made to utilize in clinical practice the marked nervous system effects previously noted [*23*] as side reactions during antituberculous therapy. The effect of iproniazid therapy was studied in mental patients [*24–26*] with varying degrees of success but it was noted to have a stimulating effect on depressed patients [*24,27*] in many cases. Iproniazid was also used in the treatment of hypertension [*28*], angina pectoris [*29*], rheumatoid arthritis [*30*] and as an appetite-stimulant in chronically ill patients [*31*]. The inhibition of monoamine oxidase [*32*] with resultant increase in the level of brain serotonin [*33*] suggested a possible physiologic explanation for the stimulating effects observed with iproniazid therapy [*34*]. It was thus popularized as a "psychic energizer" and its use became widespread.

Instances of hepatitis occurring during the administration of iproniazid and attributed to its administration began to be reported. Scherbel [*30*] noted two cases of "toxic hepatitis." De Verteuil and Lehmann [*24*] reported one death as a result of hepatic necrosis. Zetzel and Kaplan [*35*] presented a detailed report of three cases with one death and mentioned two additional cases. Frantz [*36*] reports one fatal case in detail and mentions a second patient who died with massive necrosis of the liver.

During the past five months, nine patients who became jaundiced during or shortly after taking iproniazid have been admitted to The Mount Sinai Hospital. This report describes these patients, with a discussion of their clinical course, laboratory findings and primary pathology.

CASE REPORTS

The laboratory findings are tabulated in Table I. Dosages of iproniazid and time-dose relationships are listed in Table II. Detailed pathological reports are included in the appropriate section.

CASE I. A. W., a fifty-five year old white woman, was first admitted to The Mount Sinai Hospital on February 1, 1958. She had been depressed for several months and, because of increasing mental symptoms, was given iproniazid (150 mg. daily) about ten weeks previous to admission. The patient had taken

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the medication irregularly. Three weeks before admission she had noted chilly sensations, intermittent abdominal distention, eructations, nausea and anorexia. Iproniazid therapy was stopped at that time. Two weeks previous to admission she had noted mild icterus, dark urine and light stools. The symptoms were progressive until the time of admission. There was no history of pruritus, previous jaundice or disease of the gallbladder. She had not received any injection of blood or blood products. Since June 1956 she had received "liver injections" and had taken "liver pills."

At the time of admission the patient was well nourished and markedly icteric but in no acute distress. The vital signs were normal. The liver was palpated 2 fingerbreadths below the right costal margin although the edge was not distinct. It was minimally tender to direct palpation and there was slight shock tenderness. The spleen was not palpated. The remainder of the physical examination was within normal limits.

Laboratory examination revealed a hemoglobin of 11.5 gm. per cent with a white blood cell count of 5,150 per cu. mm. and a normal differential. The erythrocyte sedimentation rate was 12 mm. per hour (Westergren). The urine was 4 plus positive for bile, and urobilinogen was present in a dilution of 1:40. The serum total bilirubin was 21.4 mg. per cent and the direct bilirubin was 18.8 mg. per cent. The serum albumin was 4.3 and globulin 2.6 gm. per cent. The total cholesterol was 170 mg. per cent with an esterified fraction of 108 mg. per cent. The alkaline phosphatase was 16.0 King-Armstrong units; thymol turbidity, 10.1 units; and the cephalin flocculation reaction 4 plus. The prothrombin time was 16.5 seconds (control 11 seconds). The serum muco-protein was 23.7 mg. per cent (low); acid-precipitable globulin turbidity (APG turbidity), 2.2 units (low); and zinc sulfate turbidity (ZS turbidity), 10.2 units (high).

The patient was placed at bedrest and given a low fat diet with vitamin supplements. There was an occasional temperature elevation to 100.2°F. but nausea and diminished appetite were minimal. Five days following admission the total serum bilirubin had risen to 29.2 mg. per cent. The stools were gray but contained stercobilin.

During the following week the stools became deep brown and there was virtual disappearance of symptoms. On the twelfth hospital day the serum total bilirubin had fallen to 22.0 mg. per cent and the serum glutamic oxalacetic transaminase (SGO-T) was 161 units per cc. By the twentieth hospital day there was only a trace of bile in the urine and urobilinogen was positive in a dilution of 1:80. The serum total bilirubin had fallen to 9.6 mg. per cent. The jaundice diminished rapidly and by the twenty-sixth hospital day the total serum bilirubin was 4.6 mg. per cent; the alkaline phosphatase, 10.3 King-Armstrong units; thymol turbidity, 4.6 units; and cephalin flocculation test, 2 plus. The patient was discharged asymptomatic on the thirtieth hospital day to continue convalescence at home.

CASE II. F. N., a fifty-nine year old white woman, was admitted to The Mount Sinai Hospital on March 25, 1958. For one week previous to admission the patient had noted decreasing appetite, mild constipation and darkening of the urine. Three days before admission she was noted to be icteric. There was no fever, nausea, emesis or pruritus.

The patient had had rheumatic heart disease with auricular fibrillation and hepatosplenomegaly since 1948. In addition she had thyrotoxicosis and had received radioactive iodine in 1952 and 1956, with disappearance of symptoms. She had continued to receive an occasional mercurial injection and oral digoxin. A few months before admission she had started to take Diuril,® 0.5 gm. daily. For about four weeks before admission she had taken iproniazid, 50 mg. daily, and had continued this until the time of admission.

Physical examination revealed a deeply icteric white woman in no acute distress. There was a slow auricular fibrillation at a rate of 80 per minute. The temperature was 100.2°F. The heart was enlarged to the left. The liver was slightly tender, firm and smooth. On inspiration it descended 6 fingerbreadths below the right costal margin and across the midline into the upper left quadrant. The spleen was firm, non-tender and descended 3 fingerbreadths below the left costal margin. The remainder of the physical examination was within normal limits.

Laboratory examination revealed a mild leukopenia with a normal differential and a hemoglobin of 12.4 gm. per cent. The urinary bile was 4 plus with urobilinogen present in a dilution of 1:40. The stool was grayish-brown and positive for stercobilin. The serum total bilirubin was 23.2 mg. per cent with a direct fraction of 12.2 mg. per cent. The alkaline phosphatase was 15.8 King-Armstrong units, the cephalin flocculation reaction was 3 plus and thymol turbidity was 3.7 units. The prothrombin time was 15 seconds (control 12 seconds).

The patient was placed at bedrest and given a high carbohydrate-low fat diet with moderate salt restriction, and digitalis was administered. The symptoms were minimal: slight nausea, mild weakness and occasional pruritus. There was one episode of postural hypotension. She remained afebrile with an occasional elevation in rectal temperature to 100.2°F. Her appetite was only slightly impaired in spite of rapidly progressing icterus. Six days after admission the serum bilirubin was 42 mg. per cent and five days later it had risen to 46 mg. per cent. The alkaline phosphatase was 17.2 King-Armstrong units, the cephalin flocculation reaction was 2 plus. The stool varied from light brown to clay colored. The patient

TABLE I

SUMMARY OF LABORATORY DATA IN NINE CASES OF IPRONIAZID HEPATOTOXICITY

Case, Sex, Age (yr.)	Date (1958)	Duration* of Illness (days)	Hemogram		Blood Chemical Findings														Urine	
			Hemoglobin (gm. %)	White Blood Cells (per cu. mm.)	Bilirubin (mg. %)		Protein (gm. %)			Cephalin Flocculation	Thymol Turbidity (units)	Cholesterol (mg. %)		Alkaline Phosphatase K-A u.	SGO-T (unit/cc.)	Globulins†			Prothrombin Patient/Control (seconds)	Bile	Urobilinogen
					Total	Direct	Total	Albumin	Globulin			Total	Ester			M (mg. %)	APG turb.	ZS turb.			
I, (A. W.), F, 55	1/31	21	11.5	5150	21.4	18.8	6.9	4.3	2.6	4+	10.1	170	108	16.0	....	....	....	....	16.5/11.0	...	.....
	2/3	24	11.3	6200	....	....	...	...	...	3+	9.1	313	177	21.7	....	23.7	2.2	10.2	.....	4+	1:20
	2/5	26	12.4	.....	29.2	18.0	7.4	3.8	3.6	4+	....	...	...	....	....	....	...	....	19.5/11.0	4+	1:20
	2/12	33	....	.....	22.0	13.0	7.0	3.6	3.4	3+	....	250	145	16.1	161	....	...	....	.....	2+	1:40
	2/19	40	12.0	7650	9.6	5.4	...	...	...	...	....	282	182	11.8	162	27.5	3.0	10.2	15.0/12.0	Tr.	1:80
	2/26	47	....	.....	4.2	3.4	...	...	...	2+	....	...	...	10.3	....	20.0	4.5	9.0	.....	...	.....
II, (F. A.), F, 59	3/26	8	12.4	3500	23.2	12.2	...	...	...	3+	..7	...	...	15.8	....	....	...	....	15.0/12.0	4+	1:40
	3/31	13	12.5	4500	42.0	22.4	...	...	...	...	....	...	...	....	....	....	...	....	.....	0	1:20
	4/5	18	....	.....	46.0	26.6	...	...	...	2+	....	292	198	17.2	....	....	...	....	.....	...	.....
	4/11	24	....	.....	46.'	25.4	...	...	...	...	....	...	...	....	420	....	..•	....	.....	...	.....
	4/16	29	12.0	5750	23.2	7.4	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....
	5/8	51	....	.....	3.0	....	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....
III, (M. D.), M, 49	3/14	6	13.9	4650	12.8	7.8	6.8	3.9	2.9	1+	....	210	160	19.1	....	32.6	3.7	4.5	.....	4+	1:160
	3/18	10	....	.....	22.4	12.8	...	...	...	...	....	...	...	....	14	....	...	....	.....	3+	1:40
	3/25	17	14.4	8600	25.6	15.2	7.5	3.6	3.9	4+	....	...	...	11.4	....	15.8	2.0	17.0	'8.0/11.5	4+	1:40
	4/1	24	14.4	11750	36.0	20.4	7.8	3.7	4.1	3+	....	280	254	12.6	147	....	...	....	13.0/12.0	4+	1:40
	4/8	31	....	.....	27.2	14.2	...	...	...	...	....	...	...	...	59	....	...	....	.....	4+	1:10
	4/15	38	....	.....	11.6	6.2	...	...	...	...	....	...	...	....	....	....	...	....	.....	0	1:40
	4/22	45	....	.....	6.4	4.2	...	...	....	4+	....	...	...	....	....	....	...	....	.....	...	.....
	5/6	59	....	.....	3.0	1.4	...	...	...	0	....	...	...	....	47	....	...	....	.....	...	.....
	5/13	66	....	.....	1.3	0.8	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....
IV, (E. G.), F, 55	4/22	80	....	.....	12.8	4.6	6.9	3.8	3.1	2+	....	224	160	18.0	2250	....	...	....	.....	...	.....
	5/13	101	....	.....	6.2	4.6	7.5	3.9	3.6	3+	....	240	...	17.0	600	....	...	....	.....	...	.....
	6/10	129	....	.....	2.2	1.4	7.7	4.0	3.7	3+	....	...	...	18.0	....	....	...	....	.....	...	.....
V, (B. C.), F, 55	3/25	6	12.4	6350	10.8	6.7	...	...	...	...	....	...	...	....	....	....	...	....	.....	2+	1:20
	3/27	8	....	.....	23.4	12.0	...	...	...	2+	6.6	283	179	13.7	100	....	...	....	15.0/12.0	2+	1:40
	4/3	15	11.4	7700	21.4	10.8	6.2	3.4	2.8	...	5.8	238	...	15.4	....	29.4	2.7	5.0	.....	3+	0
	4/7	19	....	.....	27.2	14.0	6.7	...	...	...	7.8	268	...	14.8	....	....	...	....	16.5/12.0	3+	0
	4/11	23	12.0	16100	....	....	...	...	...	...	....	...	...	....	....	....	...	....	17.5/12.5	4+	1:10
	4/19	31	....	.....	16.6	10.8	...	...	...	1+	....	...	...	11.5	....	....	...	....	13.5/12.0	2+	1:40
	4/28	40	....	.....	9.2	5.4	...	...	...	...	....	...	...	....	....	....	...	....	15.0/12.0	Tr.	1:40
	5/2	44	12.0	7100	7.6	4.8	...	...	...	...	....	...	...	....	....	....	...	....	.....	Tr.	1:40
	5/9	51	12.2	6000	5.2	3.2	...	...	...	...	....	...	...	....	....	....	...	....	12.0/12.0	...	.....
	5/16	58	....	8900	3.6	2.0	...	...	...	2+	7.7	...	...	11.8	....	....	...	....	.....	...	.....
	5/27	69	....	.....	1.7	1.0	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....
	6/7	80	12.4	9350	1.8	0.8	7.3	3.0	4.3	3+	7.3	260	180	11.0	....	....	...	....	.....	...	.....

VI, (F. T.), F, 68	5/7	5	12.2	8900	8.0	4.7	6.8	3.8	3.0	1+	1.0	290	170	22.9	450	36.8	6.7	1.	15.0/11.0	4+	1:40
	5/9	7	12.7	7500	....	....	...	...	...	...	....	...	...	22.3	500	....	...	....	.....	3+	1:20
	5/12	10	....	.....	25.4	16.2	...	...	...	4+	....	...	...	18.4	....	16.6	5.7	2.7	.....	...	.....
	5/15	13	12.2	8500	32.6	19.0	6.7	4.1	2.6	3+	1.0	250	130	14.2	490	....	...	....	.....	4+	1:20
	5/23	21	....	.....	22.8	11.6	6.5	3.7	2.8	...	1.0	277	149	17.2	....	....	3.2	3.2	15.0/12.5	1+	1:40
	5/29	27	12.4	14250	9.4	8.3	6.4	3.5	2.9	1+	1.6	386	216	12.5	195	25.0	4.5	2.7	14.0/12.0	1+	1:10
	6/9	38	12.0	6400	7.0	4.0	...	...	...	1+	....	...	...	16.0	310	....	...	....	14.0/12.0	...	.....
	6/16	45	10.9	4600	3.5	1.7	6.7	3.1	3.6	1+	2.8	263	184	9.1	57	....	3.0	6.2	.....	...	.....
	6/20	49	10.6	7900	....	....	...	...	...	...	....	...	...	....	....	52.9	5.0	6.7	.....	...	.....
	6/27	56	12.2	5300	1.5	0.9	6.7	3.8	2.9	0	2.2	310	250	10.0	85	....	6.7	6.7	14.0/12.5	...	.....
	7/3	62	11.9	7300	....	....	...	...	...	...	....	...	...	....	....	....	...	....	.....	0	1:40
	7/8	67	....	.....	1.2	0.6	6.8	3.6	3.2	2+	....	303	228	10.0	58	....	...	....	13.0/12.5	...	.....
VII, (H. S.), F, 74	5/22	22	12.9	12000	29.4	16.8	7.6	3.0	4.6	2+	....	240	158	15.8	740	....	...	....	15.0/13.0	4+	1:10
	5/24	24	....	.....	....	....	...	...	...	...	....	...	...	....	....	....	...	....	.....	4+	0
	5/26	26	....	.....	31.4	17.7	7.5	2.9	4.6	4+	3.1	...	...	20.0	760	....	2.2	8.5	.....	...	.....
	5/29	29	13.6	11150	....	....	...	...	...	...	....	...	...	....	....	25.0	2.7	10.2	.....	4+	1:10
	6/4	35	....	.....	15.8	10.1	6.9	2.5	4.5	...	3.0	160	...	16.3	....	13.9	2.7	8.0	18.5/13.0	4+	1:20
	6/11	42	12.4	10500	17.2	9.6	7.1	3.6	3.5	...	....	...	...	17.2	....	....	...	....	15.0/12.0	...	.....
	6/16	47	....	.....	11.6	5.9	6.9	2.5	4.4	4+	3.2	207	119	15.0	....	....	2.2	10.2	.....	...	.....
	6/20	51	11.6	8050	7.6	4.2	6.9	2.5	4.4	2+	4.0	225	...	12.0	....	35.3	2.2	13.0	15.0/12.5	0	1:80
	6/27	58	....	.....	4.6	2.8	7.9	3.2	4.7	3+	3.7	250	...	11.9	122	23.5	5.0	6.7	14.0/12.5	0	1:20
	7/3	64	....	.....	4.3	2.6	...	...	...	3+	....	...	...	....	....	....	...	...	.....	...	.....
	7/8	69	....	.....	3.3	2.0	...	...	...	...	....	...	...	....	....	....	...	....	.....	0	1:20
VIII, (I. S.), F, 71	5/12	16	12.4	10550	31.0	19.4	7.5	3.5	4.0	3–4+	....	255	130	22.2	460	....	...	....	21.5/12.0	3+	1:40
	5/14	18	12.4	10250	30.8	15.2	...	...	...	...	....	...	...	....	....	11.1	2.7	10.7	27.0/12.5	4+	1:80
	5/19	24	13.6	.....	....	....	...	...	...	...	5.7	...	...	....	235	....	...	....	27.5/11.0	...	.....
	5/21	26	13.4	.....	30.8	15.6	...	...	...	...	....	...	...	....	....	....	...	....	24.0/12.5	...	.....
	5/26	31	....	.....	32.6	18.9	5.8	2.8	3.0	...	....	...	...	....	....	....	...	....	16.0/13.0	...	.....
	5/29	34	12.4	13400	....	....	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....
IX, (M. N.), F, 82	6/4	15	....	.....	22.6	12.9	6.1	...	...	4+	....	257	166	16.9	....	....	...	....	.....	...	.....
	6/18	29	15.0	13950	24.4	14.6	6.7	3.3	3.4	4+	2.8	175	...	15.3	183	26.5	2.7	9.0	15.0/13.0	4+	1:40
	6/20	31	....	.....	24.0	10.0	6.6	3.3	3.3	...	....	...	...	....	....	....	...	....	.....	3+	1:20
	6/23	34	15.0	30500	24.0	18.0	...	...	...	...	....	...	...	12.9	213	....	...	....	.....	3+	1:10
	6/25	36	14.1	18350	23.6	12.4	6.9	3.5	3.4	3+	1.6	...	...	....	....	....	...	....	22.0/12.5	...	1:20
	7/1	42	....	24050	....	....	...	...	...	...	....	...	...	....	....	....	...	....	.....	...	.....

* Calculated from onset of symptoms.

† Serum globulin fractions [*37*]. M. = Mucoprotein by method of Simkin [*38*] (25% of alpha-1 globulin) (Normal: 48–75 mg. per cent in males, 40–70 mg. per cent in females). APG turb. = Acid precipitable globulin turbidity by method of Greenspan [*39*] (75–90 per cent of alpha-2 plus beta globulin) (Normal: 4–8 units). ZS turb. = Zinc sulfate turbidity method of Kunkel [*40*] (90 per cent of gamma globulin) (Normal: 4–8 units).

TABLE II
IPRONIAZID TIME-DOSAGE DATA

Case No.	Interval from First Dose to Onset of Symptoms	When Stopped in Relation to Symptoms	Daily Dose (mg.)	Number of Days Largest Dose Taken	Estimated Maximum Total Dose (mg.)
I	49 days	At onset	150	?	7,350
II	28 days	1 week after onset of icterus	50	28	1,400
III	26 days	2 days after onset of icterus	25	26	650
IV	27 days	2 days after onset of icterus	100–150	?	4,050
V	58 days (first course)	28 days before onset of icterus	50–100	9	1,950
	6 days (second course)	At onset	50	6	300
VI	33 days (first course)	18 days before onset of icterus	75–150	2	1,125
	12 days (second course)	3 days after onset of icterus	50–100	9	1,100
VII	27 days	Probably at onset	50	20	1,000
VIII	81 days	8 days before onset	10–50	67	3,400
IX	120 days (first course)	50 days before onset	25–100	7	2,950
	14 days (second course)	With onset of icterus	25–50	7	600
I*	Approx. 2 mo.	7 days after onset of icterus	150	(approx. 75)	11,250
II*	?	?	25	?	1,075
III*	Approx. 3 mo. (first course)	Approx. 2½ months before onset	150	7	1,050
	1 day (second course)	3 days after onset	75	4	300

* Cases of Zetzel and Kaplan [35].

was given 60 mg. of prednisone in a two-day period. On the sixteenth hospital day the serum bilirubin was still 46 mg. per cent and the SGO-T was 420 units per cc. The stool then became deep brown and five days later the serum bilirubin had fallen to 23.3 mg. per cent. The patient was virtually asymptomatic and was discharged from the hospital on the twenty-third day.

Under the care of her private physician she was kept at bedrest at home, receiving only vitamin supplements. Three weeks following discharge she was asymptomatic with a serum bilirubin of 4.0 mg. per cent. The hepatosplenomegaly was unchanged and was attributed to her heart disease, having been present prior to the present illness.

Comment: In the preceding two cases the severe degree of jaundice was markedly out of proportion to the mild symptomatology. The next patient demonstrated essentially the same laboratory findings and, although treated initially in a similar manner, had quite severe symptoms and signs of encephalopathy.

CASE III. M. D., a forty-nine year old white man, was first admitted to The Mount Sinai Hospital on November 10, 1957. Because of intractable severe angina pectoris of five years' duration, a bilateral internal mammary artery ligation was performed. Convalescence was uneventful and the patient was discharged five days later. Venepunctures were performed in the course of this admission but the patient did not receive any injection of blood or blood products.

There was no apparent improvement in the anginal symptoms and the patient continued taking nitroglycerine, Nitroglyn® and Demerol,® as he had for many months previously. About February 15 he began taking iproniazid, 25 mg. daily, and continued until his second admission on March 13. Five days previous to this admission he had noted postprandial nausea, anorexia, frequent eructations and generalized pruritus. Two days before admission his urine became dark although the stool remained brown. He had no chills or fever.

Physical examination revealed a well nourished, obviously icteric white man in no acute distress. The vital signs were normal. The liver edge was palpated two fingerbreadths below the right costal margin; it was smooth and slightly tender, and there was no shock tenderness. The remainder of the physical examination was within normal limits.

Laboratory examination revealed a normal hemogram. The erythrocyte sedimentation rate was 15 mm. per hour (Westergren). The urine was 4 plus positive for bile, and urobilinogen was present in a dilution of 1:160. The serum total bilirubin was 12.8 mg. per cent with a direct fraction of 7.8 mg. per cent. The serum albumin was 3.9 and serum globulin 2.9 gm. per cent. The total serum cholesterol was 210 mg. per cent with an esterified fraction of 160 mg. per cent; SGO-T was 14 units per cc.; the serum alkaline phosphatase, 19.1 King-Armstrong units; and the cephalin flocculation reaction, 1 plus. The prothrombin time was 18 seconds (control 11.5 seconds). The serum mucoprotein was 32.6 mg. per cent (low); APG turbidity, 3.7 units (low); and ZS turbidity, 4.5 units (normal).

The patient was placed at bedrest and given a low fat-high carbohydrate diet with vitamin supplements. Nausea and anorexia were severe and intravenous fluids were given as needed. Five days following admission the total serum bilirubin had risen to 22.4 mg. per cent. Administration of aristocort, 4 mg. every six hours, was started. Three days later the patient complained of diplopia and vertigo and was noted to have slurred speech with a slight flapping tremor. The administration of aristocort was discontinued and ACTH, 20 to 60 units, was given intermittently in the intravenous fluids. The protein intake was markedly restricted and neomycin was given, 0.5 gm. every six hours. Nausea, anorexia and occasional emesis persisted during the next ten days. The jaundice deepened and on April 1 the serum total bilirubin was 36.0 mg. per cent, the urinary bile varied from 2 to 4 plus positive and the urobilinogen was persistently positive in a dilution of 1:40, the cephalin flocculation reaction was 3 to 4 plus and the SGO-T rose to 147 units per cc. The serum albumin was 3.7 and globulin 4.1 gm. per cent. The serum mucoprotein fell to 15.8 mg. per cent, with a fall in the APG turbidity to 2.0 units and a rise in the ZS turbidity to 17.0 units. The white blood cell count rose to 11,750 per cu. mm. with a slight shift to the left and a relative lymphopenia. The encephalopathy fluctuated in intensity but was never severe. The liver remained tender and palpable 2.5 fingerbreadths below the right costal margin. There was no fever.

The patient was started on a regimen of medrol, 8 mg. every six hours. Simultaneously, the signs of encephalopathy cleared. Within a few days his depression and nausea disappeared and his appetite returned to normal. The administration of neomycin was stopped, and he was given a regular diet which was well tolerated. On April 8 the serum total bilirubin was 27.2 mg. per cent. The jaundice then cleared rapidly and by April 29 the serum total bilirubin was 3.0 mg. per cent.

The administration of Nitroglyn and nitroglycerine was reinstituted because of anginal symptoms. The patient continued to improve symptomatically with slow but progressive return of strength. The dosage of medrol was slowly decreased and ambulation started. By the middle of May the liver was no longer palpable. On May 6 a cephalin flocculation test was negative. On May 17, the bromsulphalein retention was 5 per cent. After sixty-six hospital days the patient was discharged, still receiving medrol, 2 mg. twice daily, and on a regimen of limited activity.

Comment: The prolonged period of morbidity and long duration of the jaundice were apparent in all the cases which we observed. The next patient came to our attention after she had passed the peak of her icterus. She had been hospitalized at another institution for eight weeks but at the time of her discharge was still markedly icteric.

CASE IV. E. G., a fifty-five year old white woman, had been treated for arteriosclerotic heart disease for two years with digitalis, ammonium chloride, and an occasional mercurial injection. For six months previous to the present illness she had received nitroglyn periodically. From January 10, 1958 to February 6, 1958 she had taken iproniazid, 100 to 150 mg. daily, for anginal symptoms. On February 1 she noted diminishing appetite, pruritus and nausea. On February 4 she was noted to be icteric and was hospitalized (records are not available). She was told that she had hepatitis and was given steroids in small

doses. Her jaundice diminished but did not disappear and, after eight weeks of hospitalization, she was discharged.

On April 22 she was first seen by a member of the staff of The Mount Sinai Hospital. She complained of persistent weakness, anorexia and pruritus. The jaundice had not changed since the time of discharge, and the patient was still markedly icteric. The liver was palpated 1 fingerbreadth below the costal margin; there was no tenderness and the spleen was not felt.

Laboratory examination revealed a total serum bilirubin of 11.8 mg. per cent. The alkaline phosphatase was 18 King-Armstrong units; the serum albumin was 3.8 and globulin 3.1 gm. per cent; a cephalin flocculation test was 2 plus with an SGO-T of 2,250 units per cc. The patient was kept at bedrest and given mild sedation in addition to prednisone, 5 mg. three times a day. Her appetite improved and nausea disappeared. Her stools became darker and the urine became lighter.

By May 13 the serum total bilirubin had fallen to 6.2 mg. per cent and the SGO-T was 600 units per cc. On May 22 progressive ambulation was begun. The liver was no longer palpable. By June 10 her serum total bilirubin was 2.2 mg. per cent. A cephalin flocculation test was 3 plus. She was aymptomatic but still receiving steroids more than one hundred days after the onset of her illness.

Comment: Although the routine laboratory studies in our series invariably suggested hepatocellular disease, a "cholangiolitic" or obstructive phase is often present at the height of the jaundice. The patients are frequently in the age group in which extrahepatic obstructive lesions are common. In the next case, a long history of vague abdominal symptoms, clay colored stools and disappearance of urobilinogen from the urine suggested the possibility of extrahepatic obstruction and an exploratory laparotomy was performed.

CASE V. B. C., a fifty-eight year old white woman, was admitted to The Mount Sinai Hospital on March 25, 1958. Since August 1957 the patient had complained of vague squeezing epigastric pain. In the latter part of November she began having postprandial nausea and emesis. In December she was admitted to another hospital and treated with intravenous fluids and a single injection of Sparine.® An oral cholecystogram demonstrated a normally functioning gallbladder without stones. A barium examination of the upper gastrointestinal tract revealed no abnormalities. The patient was discharged without a definitive diagnosis still complaining of pain radiating into both upper quadrants.

On January 20, in view of an apparent depression, the patient was started on a regimen of iproniazid, 100 mg. daily. On January 29 this was reduced to 50 mg. daily which the patient took irregularly for three weeks. On March 13 the patient again started taking iproniazid, 50 mg. daily, but for only six days. During this time the urine became darker and the stools were lighter. She had lost 12 pounds in the preceding six months. The administration of iproniazid was stopped on March 19. Anorexia, nausea and emesis became severe and three days prior to admission on March 25 she was noted to be icteric.

On admission, physical examination revealed a markedly icteric white woman who appeared lethargic and depressed. There was a slowness of response to questions and the patient spoke in a monotone. The vital signs were normal. There was minimal superficial tenderness in the epigastrium and upper right quadrant but no shock tenderness. Neither the liver nor spleen was palpable. The remainder of the physical examination was within normal limits.

Laboratory examination revealed a hemoglobin of 12.4 gm. per cent with a normal white blood count and differential. The erythrocyte sedimentation rate was 9 mm. per hour (Westergren). The urine was 2 plus positive for bile, with urobilinogen present in a dilution of 1:20. The serum total bilirubin was 23.4 mg. per cent with a direct fraction of 12.0 mg. per cent. The alkaline phosphatase was 13.7 King-Armstrong units; the serum albumin was 3.4 with globulin 2.8 gm. per cent; the SGO-T was 100 units; the cephalin flocculation reaction, 2 plus; and thymol turbidity, 5.4 units. The serum mucoprotein was 29.4 mg. per cent (low); APG turbidity, 2.7 units (low); and ZS turbidity, 5.0 units (normal). The prothrombin time was 15 seconds (control 12 seconds). The stool was light brown.

The patient was given a low fat diet. Because of anorexia, nausea and occasional emesis, intravenous fluids were administered as needed. Various vitamin K preparations were also given. Weakness, lethargy and depression were quite severe. She remained afebrile.

Six days following admission the stools were noted to be clay colored and, although the urinary bile was 3 plus positive, no urobilinogen was detected on repeated examinations. The jaundice deepened and by the twelfth hospital day the serum total bilirubin was 27.4 mg. per cent. The thymol turbidity rose to 7.8 units. A diagnosis of extrahepatic obstruction was considered likely and on the fourteenth hospital day an exploratory laparotomy was performed.

The liver was small without gross nodularity. The gallbladder was normal, no stones were palpated and there was no dilatation of the common bile duct. A liver biopsy (Fig. 1) showed diffuse hepatitis with isolated cell necrosis and regeneration and diffuse inflammatory reaction particularly in the portal areas. The picture could not be differentiated from that seen in viral hepatitis.

Following surgery the patient was given intravenous

fluids with potassium chloride, sodium chloride, penicillin, vitamins and 200 mg. of hydrocortisone daily. Two days postoperatively an improvement in the mental status was noted. The dosage of hydrocortisone was slowly decreased, intravenous fluids were discontinued on the eighth postoperative day and the patient was given cortisone acetate, 25 mg. intramuscularly three times daily, and a high protein-low fat diet with supplemental potassium and vitamin K. By the twelfth postoperative day the serum total bilirubin had fallen to 16.6 mg. per cent. The urine was 2 plus positive for bile and urobilinogen was now present in a dilution of 1:40. Prednisone, 5 mg. three times daily, was now substituted for cortisone. On the twenty-first postoperative day penicillin was discontinued and two days later the patient began having fever daily with temperatures to 100 to 101°F. The dosage of prednisone was gradually diminished and finally discontinued on the thirtieth postoperative day. Two days later the patient had a temperature elevation to 103.8°F. without localizing symptoms. In spite of extensive investigation the cause of the fever was not determined. She was given Achromycin,® 250 mg. every six hours. For one week she continued having daily elevations in temperature to 102°F. followed by a gradual lysis and after two weeks she was again afebrile.

After the initial rapid fall in serum total bilirubin, there was a more gradual decline so that at the time of discharge the serum total bilirubin was 1.8 mg. per cent. Mild nausea and upper right quadrant discomfort, like that present during the eight month period preceding admission, was still present at discharge. Physical examination was unremarkable and failed to reveal any stigmas of cirrhosis.

Comment: The usual absence of significant fever in these cases was quite remarkable and will be commented upon further. A period of high fever without apparent cause occurring simultaneously with withdrawal of steroids was noted in the preceding case. A similar sequence of events was noted in the next case. In neither instance was any symptomatic or chemical relapse noted with or following the febrile episode.

CASE VI. F. T., a sixty-eight year old white woman, had a history of depression with numerous somatic complaints for many years. She had received electric shock therapy and psychotherapy with indifferent results. On April 1, 1958 she was given iproniazid, 150 mg. for two days; on April 3 this dosage was reduced to 75 mg. daily because of excessive drowsiness and on April 14 the drug was discontinued. Because of persistent severe symptoms iproniazid therapy was started again on April 21 at a dosage of 100 mg. daily, reduced to 50 mg. daily on May 2



FIG. 1. Case v. Surgical specimen showing diffuse inflammatory reaction and areas of necrosis. In other areas there are degenerative liver cells.

because of postural hypotension. On May 3 the patient noted darkening of her urine and increase in her usual anorexia. On May 6 she noted that her eyes were yellow. Administration of the drug was stopped and she was admitted to The Mount Sinai Hospital on that day.

There was no history of fever, nausea or pruritus. The patient had received a single intramuscular injection three weeks previous to admission. She had multiple abdominal complaints for many years but had occasional episodes of severe pain requiring the administration of narcotics. Five years before she had been told that she had "gall stones."

Physical examination revealed an icteric white woman in no acute distress. The vital signs were normal. Liver dullness was percussed 3 fingerbreadths below the right costal margin; there was no spontaneous tenderness but shock tenderness was occasionally elicited.

Laboratory examination on admission revealed a normal hemogram and erythrocyte sedimentation rate. The test for urinary bile was 4 plus positive and urobilinogen was detectable in a dilution of 1:40. The serum total bilirubin was 8 mg. per cent with a direct fraction of 4.7 mg. per cent. The alkaline phosphatase was 22.9 King-Armstrong units; cephalin flocculation reaction, 1 plus; thymol turbidity, less than 1.0 units; and SGO-T, 450 units per cc. The serum albumin was 3.8 with globulin 3.0 gm. per cent. The prothrombin time was 15 seconds (control 11 seconds). The serum mucoprotein was 36.8 mg. per cent (low); APG turbidity, 6.7 units (normal); and ZS turbidity, 1.7 units (low).

The patient was placed at bedrest and given pyridoxine, 100 mg. twice daily, in addition to multiple vitamins, Mephyton,® and a low fat-high carbohydrate diet. Anorexia continued and nausea became evident. She noted pruritus and increased weakness. Her urine remained dark, the stool was noted to be light. She remained afebrile.

Her icterus rapidly progressed and on May 15 her

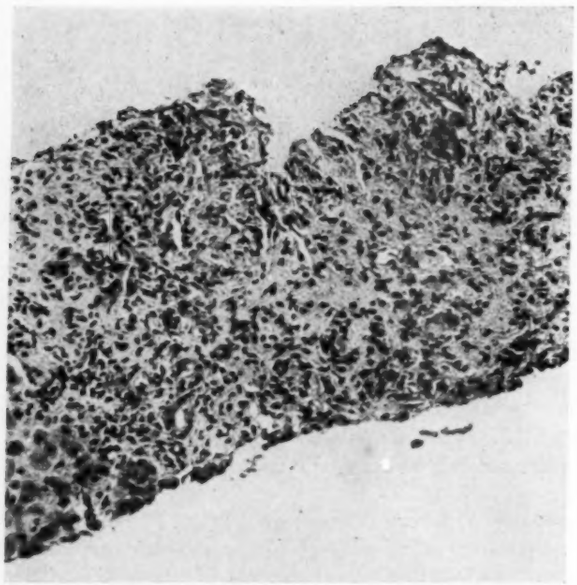


FIG. 2. Case VII. Biopsy specimen showing massive necrotic hepatitis with broad bands of collapse and diffuse mononuclear infiltration.

serum total bilirubin was 32.6 mg. per cent. The cephalin flocculation reaction was now 3 plus and the serum mucoprotein level had fallen to 16.6 mg. per cent. The following day she was started on a regimen of medrol, 4 mg. four times daily. On May 20, because of a persistently low serum gamma globulin, she was given gamma globulin, 2 cc. daily. Except for some decrease in her depression, no other symptomatic change was noted but her icterus decreased rapidly. One week later her serum total bilirubin was 22.8 mg. per cent. On May 27 the dosage of medrol was decreased to 4 mg. three times daily. Four days later the serum total bilirubin had fallen to 9.4 mg. per cent and the serum mucoprotein had risen to 25.0 mg. per cent. A leukocytosis of 14,250 cells per cu. mm. with a relative lymphopenia was noted.

On June 2 administration of medrol and gamma globulin was stopped. On June 5 she had a temperature elevation to 101°F. and thereafter a daily fever with temperatures of 102.6 to 103°F. until June 10. There were no localizing findings or evidence of infection, and multiple blood cultures were negative. The white blood cell count had returned to normal. The patient's general condition did not change. From June 11 to July 3 she continued having fever daily with temperatures of 100.2 to 101°F. She was then afebrile for the last week of our observation. The jaundice cleared rapidly and on June 16 the serum total bilirubin was 3.5 mg. per cent with a SGO-T value of 57 units per cc. The liver was no longer palpable.

The patient complained of mild anorexia, gaseous distention, eructations and headaches, similar to her complaints for many years. On July 8 the serum total bilirubin was 1.2 mg. and ambulation was started. The patient was discharged after seventy-one days.

CASE VII. H. S., a seventy-four year old white woman, was admitted to The Mount Sinai Hospital on May 21, 1958. Three weeks before admission she had noted the gradual onset of anorexia. A week later her urine had become darker and her stools lighter. Four days later she had noted jaundice and pruritus. Weakness and weight loss were additional complaints.

The patient had been in a concentration camp during the Second World War, at which time she had malnutrition. There was no recent history of injections or transfusions. On April 3, 1958 the patient had started taking iproniazid, 50 mg. daily, but may have taken her medication on an irregular schedule. No more than twenty tablets were ingested up to the time of admission.

On admission, physical examination revealed a jaundiced white woman in no acute distress. The vital signs were normal. The liver and spleen were not palpated and there was no abdominal tenderness. There were no stigmas of cirrhosis and the remainder of the physical examination was within normal limits.

Laboratory examination revealed a mild leukocytosis with a normal differential. The urine was 4 plus positive for bile and urobilinogen was detectable in a dilution of 1:20. The serum total bilirubin was 29.4 mg. per cent; the serum albumin was 3.0 and globulin 4.6 gm. per cent; the alkaline phosphatase, 15.8 King-Armstrong units; the cephalin flocculation reaction, 2 plus and the SGO-T, 740 units per cc.

The patient was placed at bedrest and given a low fat diet with multiple vitamin supplements. She was relatively comfortable, complaining only of mild pruritus, anorexia and weakness. Her serum total bilirubin rose to its maximum of 31.4 mg. per cent five days after admission. The serum mucoprotein was 25.0 mg. per cent (low); APG turbidity, 2.7 units (low); and ZS turbidity, 10.2 units (high). The urine bile was 4 plus positive but urobilinogen was absent on one occasion in two other specimens. The patient remained afebrile. Her appetite improved, and weakness and pruritus diminished after two weeks of hospitalization.

A liver biopsy specimen (Fig. 2) was obtained on June 10, 1958 and showed acute severe hepatitis with focal massive collapse and beginning formation of septums. The presence of acidophilic bodies, the type of exudate and the marked regeneratory features were identical with those found in viral hepatitis.

The patient was soon virtually asymptomatic and after one month of hospitalization the serum total bilirubin was 7.6 mg. per cent. The SGO-T was 119 units per cc., the cephalin flocculation reaction remained at 3 plus. The serum albumin was 2.5 and globulin 4.4 gm. per cent.

The patient was slowly ambulated and, after forty-seven hospital days, was asymptomatic but her serum

total bilirubin was 3.3 mg. per cent. Her activity is still restricted and convalescent home care is anticipated.

Comment: Among the nine cases presented here, there were two deaths. Until these patients went into coma there was no clear indication, either clinically or by means of routine laboratory examinations, that their course would be more severe than those who survived.

CASE VIII. I. S., a seventy-one year old white woman, was admitted to The Mount Sinai Hospital on May 10, 1958. Three weeks prior to admission a mild upper respiratory infection had developed with low grade fever; about a week later she had noted anorexia and nausea. A few days afterwards she became jaundiced, with darkening of the urine and occasional clay colored stools.

For one year the patient had taken a reserpine preparation, 0.5 mg. daily, for mild hypertension. She had also received vitamin B_{12} and "liver injections" at irregular intervals. On February 4, 1958 she began to take iproniazid, 50 mg. daily, for a mild depression. On April 13 the dosage was changed to 10 mg. daily and on April 18 she stopped the medication. The past history was otherwise non-contributory.

At the time of admission the patient was well nourished, markedly icteric and complaining of mild nausea. Except for a mild hypertension, the vital signs were normal. The liver edge was palpated 1 fingerbreadth below the right costal margin. There was neither direct nor shock tenderness. The spleen was not palpated. The remainder of the physical examination was within normal limits.

On admission, laboratory examination revealed a mild leukocytosis with a shift to the left. A urine test for bile was 3 plus positive, with urobilinogen detectable in a dilution of 1:40. The serum total bilirubin was 30.0 mg. per cent with a direct fraction of 19.4 mg. per cent. The serum albumin was 3.5 and globulin 4.0 gm. per cent. The serum alkaline phosphatase was 22.2 King-Armstrong units; SGO-T, 460 units per cc.; cephalin flocculation reaction, 3 plus; and thymol turbidity, 5.7 units. The prothrombin time was 21.5 seconds (control 12 seconds). The serum muco-protein was 11.1 mg. per cent (low); APG turbidity, 2.7 units (low); and ZS turbidity, 10.7 units (high).

The patient was given a low fat diet, thiamine chloride, 100 mg. three times daily, and various vitamin K preparations orally and intramuscularly. In spite of the latter, her prothrombin time rose during the first week to 30 seconds (control 12 seconds). The patient remained afebrile and appeared to be improving clinically with increasing strength and appetite and decreasing nausea. The serum bilirubin did not change.

On the fifth hospital day administration of prednisone, 10 mg. four times daily, was begun. Three days later she complained of marked weakness and was noted to be drowsy with a flapping tremor. The liver was no longer palpable. The dietary protein intake was stopped and intravenous fluids containing large doses of vitamin mixtures and 80 to 120 units of ACTH daily were started. The patient was given neomycin, 2 gm. three times daily, with frequent enemas. The coma deepened and hydrocortisone, 300 mg. daily, was added to the intravenous fluids. By the twelfth hospital day the patient appeared more alert and less asthenic. She was able to take medication orally. The SGO-T had fallen to 235 units per cc., the prothrombin time and serum bilirubin remaining unchanged. Clinical improvement continued for two more days but on the fifteenth hospital day a flapping tremor again developed and the patient became comatose.

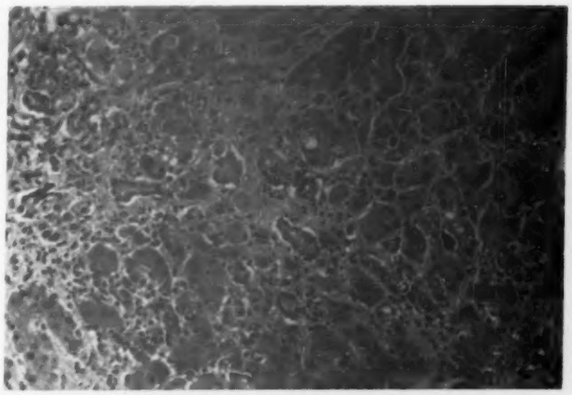


FIG. 3. Case VIII. Necropsy specimen showing areas of necrosis and bile stasis with regenerative liver cells and ductular proliferation.

During this period edema of the dependent areas and of the face developed. The blood urea nitrogen rose from 10 to 54 mg. per cent, with progressive anasarca and hypoelectrolytemia; the serum sodium fell from 123 to 110 mEq. per L. The total intake of fluid daily was 1,700 to 2,300 cc. with a daily output of less than 1,000 cc. The urine specific gravity rose to 1.020. The serum albumin was 2.8 and globulin 3.0 gm. per cent.

The patient continued in a semi-comatose state. Intravenous administration of human serum albumin on two occasions did not alter the course. On the twentieth hospital day the patient suddenly went into shock, responded transiently to nor-epinephrine, and died a few hours later.

Autopsy revealed multiple cortical cysts of both kidneys which were otherwise normal. The liver was small and finely granular. The microscopic diagnosis (Fig. 3) was subacute "submassive" necrotic hepatitis with beginning nodular regeneration and severe cholestasis. The picture was similar to that seen in cases designated as viral hepatitis.

Comment: The difficulty in maintaining water and electrolyte balance in the presence of severe hepatic insufficiency noted in Case VIII was again evident in the next patient. She followed essentially the same clinical course, remaining in a semi-comatose state for more than two weeks.

CASE IX. M. N., an eighty-two year old white woman, had been depressed for one year. On January 20, 1958 the patient had been given iproniazid, 100 mg. daily. On January 27 the dosage was reduced to 50 mg. and on February 24 to 25 mg. daily. Administration of the drug was discontinued on April 1. The depressive symptoms recurred and on May 6 she was again given iproniazid, 50 mg. daily. This was decreased to 25 mg. on May 13 and discontinued on May 23.

On May 20 the patient had noted mild nausea and darkening of the urine. Three days later she was found to be icteric. Physical examination at that time was within normal limits except for mild tenderness in the upper right quadrant.

In addition to iproniazid the patient had taken vitamin B_{12} and folic acid orally for a year and for a number of years had received monthly injections for osteoarthritis. For about forty years she had had intermittent pain in the upper right quadrant and had been on a low fat diet. An exploratory laparotomy had been performed thirty years before without any pathologic condition being noted. For a few months preceding her illness she had taken two drinks of whiskey daily.

The patient was put at bedrest at home, and given a high carbohydrate-low fat diet and vitamin supplements. Her appetite remained fair but nausea and emesis became more severe, and pruritus developed. The jaundice deepened. On June 4 the serum total bilirubin was 22.6 mg. per cent with a direct fraction of 12.9 mg. per cent. The alkaline phosphatase was 16.9 King-Armstrong units and the cephalin flocculation reaction was 4 plus. The stools were clay colored.

On June 7 the patient was started on a regimen of prednisone, 5 mg. three times daily. The icterus had progressed steadily, her appetite had diminished and weakness had become more pronounced. On June 14 she was lethargic, confused and disoriented, with a transient flapping tremor. The patient was admitted to The Mount Sinai Hospital on June 17.

On admission, physical examination revealed an acutely ill, markedly icteric white woman. She was semi-comatose, disoriented and confused. The vital signs were normal. The oropharynx was dry, with monilial patches throughout. No organs or masses were palpated and tenderness could not be elicited. There was slight pretibial edema. All extremities were flaccid but the deep tendon reflexes were normal.

Laboratory examination revealed a leukocytosis of 13,950 cells per cu. mm. with a shift to the left. The serum albumin was 3.3 with globulin 3.4 gm. per cent. The serum total bilirubin was 24.4 mg. per cent; alkaline phosphatase, 15.3 King-Armstrong units; SGO-T, 183 units per cc.; thymol turbidity, 2.8 units; and cephalin flocculation reaction, 4 plus. The prothrombin time was 15 seconds with a control of 13 seconds. The serum mucoprotein was 26.5 mg. per cent (low); APG turbidity, 2.7 units (low); and ZS turbidity, 9.0 units (high).

The patient was given intravenous fluids containing ACTH, 80 to 120 units; hydrocortisone, 200 to 300 mg.; chloromycetin 1.0 to 1.25 gm.; and mixed vitamins daily. She also received pyridoxine, 50 mg. three times daily. Frequent enemas were given. The patient then began to take fluids orally, and was given neomycin, 1.0 gm. every six hours. She was soon able to respond to stimuli. A flapping tremor became evident as the marked asthenia remitted. After six days intravenous medication was stopped. There was no significant change in the blood chemical determinations.

She was started on a regimen of prednisone, 10 mg. every six hours, and ACTH, 20 units intramuscularly twice daily. Chloromycetin therapy was discontinued. The diet was devoid of protein but carbohydrate was given in large amounts. Her clinical state fluctuated but at all times there was evidence of severe encephalopathy. Marked telangiectasia of her back, popliteal area and shoulders developed. Some anasarca was apparent. Mild hyponatremia and hypochloremia was noted at this time. Fluid and electrolyte intake was restricted in accordance with her output. From June 17 to 24 she had a daily urine volume of 1,190 to 1,540 cc. with an average daily intake 480 cc. in excess of urinary volume. The urine specific gravity rose to 1.020. From June 25 to 30 the daily urine volume fell from 680 to 360 cc. and the blood urea nitrogen rose to 53 mg. per cent. The edema did not diminish when fluid intake was restricted. There was an increase in edema without a rise in urinary output when an excess of water was given. The serum sodium and chloride fell to 114 and 80 mEq. per L., respectively. Therapy with ACTH was discontinued and prednisone, 30 mg. every six hours, was substituted. The serum bilirubin did not change. After a transient slight improvement, she lapsed into deep coma. She died on July 1 after two weeks of hospitalization.

At autopsy the liver was small, weighing 750 gm. Microscopic sections showed extensive hepatic necrosis.

ANALYSIS OF CASES

This series included eight women fifty-five to eighty-two years of age and one forty-nine year old man. All were Caucasian. Two of the women died and autopsies were performed. In two others liver biopsy specimens were available.

Predisposing Factors. None of the patients had a history of excessive alcohol intake, recent

contact with jaundiced patients, previous jaundice, contact with the usual hepatotoxins, parasitism or allergy. All were well nourished. Only one patient had pre-existing hepatosplenomegaly which was due to congestive heart failure. There was no other history of previous liver disease. In Case v there was a history of gallbladder disease but the cholecystogram was normal and the gallbladder appeared normal at exploratory laparotomy. In both fatal cases the gallbladder was normal at autopsy. In Case vi there was a history of repeated "gallbladder attacks." X-ray films of the abdomen did not reveal calculi in the five patients in whom they were obtained.

Previous Medication. None of the patients had received any previously known hepatotoxic medication or injection of blood or blood products. One patient received intravenous fluids and a single injection of Sparine® a few months prior to illness. Another patient had a venepuncture and internal mammary artery ligation. Five other patients had received intramuscular injections within the preceding six month period. Each patient was cared for by a different physician. Numerous oral medications had been taken for extended periods previously and many were continued during the illness without apparent harmful effect.

Time-Dosage Relationships of Iproniazid (Table ii). All patients received iproniazid, six for depression and three for angina pectoris. Three patients received two courses of therapy. In the six patients receiving a single course, the interval from the first dose to the onset of symptoms was twenty-six to eighty-one days (mean forty days). The dosage varied from 10 to 150 mg. daily. In a few cases the total dose was unknown because of irregularity on the part of the patient, and the maximum total dose was therefore estimated. In the six patients who received a single course, the estimated maximum total dose was 650 to 7,350 mg. with an estimated maximum average daily dose of 25 to 150 mg. (in four cases 50 mg. daily or less).

Three patients received two courses of therapy. In the first course the daily dose varied from 25 to 150 mg. The estimated maximum total dose was 1,125 to 2,550 mg. with an estimated maximum average daily dose of 42 to 86 mg. during the first course. The duration of the first course was thirteen, thirty and seventy days in these cases and medication was discontinued eighteen, twenty-eight and fifty days, respectively before the onset of symptoms. The interval from the completion of the first course to the start of the second course was six, twenty-two and thirty-six days. The estimated maximum total dose in the second course was 300 to 1,100 mg. with a daily dose of 25 to 100 mg. and an estimated maximum average daily dose of 35 to 79 mg. The interval from the first dose of the second course to the onset of symptoms was twelve, six and fourteen days. The estimated combined total dose of both courses was 2,225 to 3,550 mg.

None of the patients who received two courses of therapy were noted to be icteric or to have symptoms attributable to liver disease during the first course. Liver function tests were not carried out during or immediately after the first course. The total dose, daily dose and duration of therapy (except possibly in Case vi) of the first course were within the range noted in the six patients in whom jaundice developed after a single course. The interval between courses, except in Case vi, was apparently too great to attribute the jaundice to the first course. The duration of therapy and estimated total dosage of the second course was less than the first course in the same patient. In addition, the interval from the first dose of the second course to the onset of symptoms in patients receiving two courses was always less than the interval in patients receiving a single course. The time-dosage relationships in the cases of Zetzel and Kaplan [*35*] were compatible with this analysis. The significance will be further discussed when we consider pathogenesis.

Eight patients discontinued iproniazid therapy at the onset of symptoms or within a few days after the appearance of jaundice. Therefore the total dosage of iproniazid taken before the onset of symptoms was less than indicated in the preceding estimates. One patient stopped taking the drug eight days prior to the onset of symptoms. None of the factors of time or dosage discussed here could be related to the severity of the illness.

CLINICAL COURSE

Preicteric Period. A tabulation of the pertinent laboratory data appears in Table i. The period from the onset of symptoms until jaundice was recognized was three to seven days in seven cases and eleven days in one case. Dark urine, light stools and pruritus were frequently

noted before jaundice was recognized by the patient. The serum total bilirubin after one week of symptoms in four patients was 8.0 to 23.2 mg. per cent. These factors suggest that the preicteric period may be shorter than we have noted here.

The preicteric period was characterized primarily by gastrointestinal symptoms and a feeling of weakness and malaise. The onset varied from insidious to abrupt. Diminished appetite was noted in all patients as an early symptom. Nausea was complained of by seven of the patients but emesis occurred in only three and was generally mild. Fatty food intolerance, postprandial distention, discomfort in the upper right quadrant and constipation were occasionally noted. Only one patient had a preceding upper respiratory infection with low grade fever but the interval suggested that this may have been coincidental. There was no other documented temperature elevation. Four patients noted pruritus and all of them reported dark urine and light stools. The severity of the symptoms varied markedly and could not be correlated with the subsequent clinical course or laboratory findings.

Period of Increasing Jaundice. There was no abrupt symptomatic change with the recognition of jaundice. The symptoms already noted persisted with slowly increasing severity. Nausea and diminished appetite of varying degree were universal and pruritus appeared in one patient in whom it was not previously noted. All patients were afebrile except for a rare elevation to 100° to 102.2°F. in two cases during this period of increasing jaundice.

Serum bilirubin determinations were obtained at least twice a week during this period. In the patients who survived, maximum levels were reached on the thirteenth to twenty-sixth day of illness. The two patients who died reached a peak level on the sixteenth and twenty-eighth day, respectively, and continued to maintain this maximum level until death. Symptoms for any single patient paralleled the rise in bilirubin, being most severe at about the time of maximum jaundice. In the three patients with encephalopathy the signs of central nervous system involvement were most prominent at the time of maximum bilirubinemia. On the other hand, the level of bilirubin was no guide to the severity of illness when comparing one patient with another. Excluding Case IV, in which no early data are available, the maximum serum bilirubin was 24.4 to 46.0 mg. per cent, with an average for the eight cases of 32.4 mg. per cent. The three patients with the mildest symptoms attained levels of 29.2 to 46.0 mg. per cent. The two patients who died reached levels of 32.6 and 24.4 mg. per cent and M. D. (Case III), who had signs of encephalopathy, had a maximum level of 36.0 mg. per cent.

All patients excreted large amounts of bile in the urine. During this phase the urinary urobilinogen was either normal or slightly increased. In two patients complete absence of urinary urobilinogen was noted immediately preceding maximum bilirubinemia. All patients had light stools and on many occasions clay colored stools were noted although stercobilin was present in the few specimens examined. This transient "obstructive" pattern in patients in this age group caused concern in differential diagnosis. The frequent and unexplained finding of strongly positive guaiac reactions in the stool further complicated the problem but the laboratory studies to be discussed suggested hepatocellular disease rather than primary obstructive jaundice.

There was no evidence of significant anemia, the hemoglobin levels remaining stable throughout hospitalization. The erythrocyte sedimentation rate during this period was normal in all seven patients in whom it was measured. The initial total white blood cell count was normal in five patients. Three subsequently had a transient leukocytosis while receiving steroids. The patients with a fatal course had a persistent leukocytosis but were also receiving steroids. H. S. (Case VII) had an initial leukocytosis and was not receiving steroids but was symptomatically quite mild. The presence of a leukocytosis in any single patient was therefore not prognostically significant and the appearance of a leukocytosis in a patient receiving steroids was usual and did not indicate a worsening of the disease. A mild monocytosis and/or lymphocytosis was irregularly noted as was a shift to the left in the neutrophilic series. No significant eosinophilia was noted in any of the patients.

The serum alkaline phosphatase was consistently slightly elevated. Serum albumin and globulin levels were normal during the early weeks of illness but there was a rise in globulin and fall in albumin during or after the third week. The prothrombin time was slightly to moderately prolonged in all cases and markedly prolonged in the two fatal cases. Serum choles-

terol levels were generally within the normal range; the esterified fraction was variable.

Cephalin flocculation tests were made in all patients and during this period were consistently abnormal. Although occasional results of 1 plus were equivocal, if repeated within a few days a 3 plus or 4 plus reaction invariably was noted. The thymol turbidity during this period varied; it was elevated in three patients and normal in four patients. The serum glutamic-oxalacetic transaminase was consistently elevated but a value of more than 400 units per cc., considered diagnostic of hepatocellular disease in our laboratory [*41*], was noted in only four cases during this period. Earlier and more frequent determinations appear advisable in this regard.

The most consistent finding was a low serum mucoprotein. This was noted as early as the fifth day of illness and persisted throughout the period of increasing jaundice. The acid-precipitable globulin test usually gave low values; at no time was a high APG turbidity noted. The zinc turbidity test gave high or normal values except in Case VI in which there was an unexplained hypogammaglobulinemia. This pattern of reduced serum mucoprotein, reduced APG turbidity and high ZS turbidity is consistent with severe hepatocellular insufficiency [*37*].

Thus the routine liver function tests indicated hepatocellular disease although, as is usual in this type of problem, no single test was diagnostic. In the age group to which these patients belonged the exclusion of "surgical" jaundice was of primary immediate importance.

Period of Decreasing Jaundice. There was an initial precipitous fall in the serum bilirubin during the first seven to ten days following the maximum level noted. This was either immediately preceded by or shortly followed by marked clinical improvement, whether or not steroids were administered. The appetite improved, nausea diminished, pruritus disappeared, an improvement in the sense of well-being was noted. Hepatomegaly and liver tenderness, when previously present, were no longer apparent. The most persistent problem was weakness. Although this also improved, it persisted as a chronic complaint for a number of weeks and made subsequent ambulation a slow procedure.

The initial rapid fall in serum bilirubin was followed by a more gradual decline. In no case under our observation did the bilirubin reach a level of less than 1.0 mg. per cent although the observed duration of illness (excluding Case IV) was forty-seven to eighty days. M. D. (Case III) had a normal bromsulphalein excretion after ten weeks of illness. E. G. (Case IV) still had a significant hyperbilirubinemia after eighteen weeks of illness but since early data are not available it is not certain whether this prolonged course represents a relapse or a slow process of recovery; the latter appears more probable since no increase in jaundice was noted after the initial fall from maximum intensity.

The erythrocyte sedimentation rate, previously normal, was elevated late in the illness in the three patients in whom the determination was repeated. The serum alkaline phosphatase and prothrombin time returned to normal in the five cases in which they were followed. The cephalin flocculation reaction was variable but tended to remain positive up to the end of the period of observation. The thymol turbidity remained elevated in the two cases in which it was originally abnormal and did not change in the two cases in which the original values were normal. A rising thymol turbidity was not noted during the period of observation but the possibility of a late rise is not excluded. The serum glutamic-oxalacetic transaminase fell but remained elevated long after the bilirubinemia began to decrease. The serum total protein either did not change or increased slightly. In all four cases in which late determinations were made, a depressed albumin and elevated globulin were noted. The serum globulin fractions were followed serially in three cases. In all three the APG turbidity returned to normal. The mucoprotein remained low in two and the ZS turbidity remained high in one. Serial examinations indicated that the various protein fractions were in a changing state and had not yet attained stability at the end of the period of observation (forty-seven to 126 days of illness).

The laboratory findings in the two patients who died (Cases VIII and IX) differed from those described only in the persistence of maximum bilirubinemia for about two weeks and the development of a markedly prolonged prothrombin time. These patients had overt signs of encephalopathy and a recurrent semicomatose state. The development of azotemia, hyponatremia and hypochloremia with edema and diminished sodium excretion indicated a poor prognosis.

The observed duration of illness was forty-seven to 126 days, all patients still exhibiting mild hyperbilirubinemia and other evidences of hepatic instability, as already noted. The total period of hospitalization varied from twenty-three to seventy-five days, and one patient was still hospitalized afte. fifty-two days. None of the patients had returned to their pre-illness level of activity at the end of the period of observation covered by this report.

PATHOLOGY

A review of the pathological findings in each case will point up the histological features associated with iproniazid hepatitis.

CASE V. (Surgical biopsy specimen.) (Fig. 1.) The lobular architecture was in general preserved except in certain areas with collapse in which the portal tracts were approximated. There was diffuse liver cell damage. The cells varied in shape and staining quality, some exhibiting hydropic swelling and others transformed into acidophilic bodies. The portal tracts were poorly limited. There was an inflammatory exudate throughout the lobules. The inflammatory cells were mostly mononuclear intermixed with some eosinophilic leukocytes. Diagnosis: Acute diffuse hepatitis.

CASE VII. (Needle biopsy specimen.) (Fig. 2.) The lobular architecture was preserved except in some areas of collapse. There was diffuse liver cell damage, with many "balloon" cells and various types of clumping of the cytoplasm. Some cells had an eosinophilic protoplasm with pyknotic nuclei. Some cells showed evidences of regeneration. The portal tracts were somewhat enlarged, with collagenous membranes extending into the parenchyma. Diagnosis: Acute severe hepatitis with focal massive collapse and beginning formation of septums.

CASE VIII. (Autopsy specimen.) (Fig. 3.) The lobular architecture was distorted by broad areas of collapse. In some fields the liver plates presented a nodular arrangement. There were areas of necrosis of liver cells, which were replaced by mononuclear elements. Where the liver cells were preserved they exhibited irregular clumping of the cytoplasm. Marked bile stasis was present. The bile canaliculi were dilated, many with ramified bile plugs. In the portal tracts as well as in the collapsed areas macrophages, lymphocytes and segmented leukocytes were seen. Diagnosis: Subacute "submassive" necrotic hepatitis with beginning nodular regeneration and marked cholestasis.

CASE IX. (Autopsy specimen.) The lobular architecture was distorted by collapse. In some areas the plates were two cells thick and had a nodular appearance. There were some necrotic liver cells, others were severely damaged, some were transformed into acidophilic bodies. The bile canaliculi and some proliferated ductules were dilated and contained microcalculi. The portal tracts were clearly delineated and infiltrated by inflammatory elements which included a few segmented leukocytes, lymphocytes and macrophages. Diagnosis: Massive necrotic subacute hepatitis with beginning nodular regeneration and marked intrahepatic cholestasis.

The predominant feature in the two autopsies was the hepatic damage, suggesting that iproniazid in these patients was primarily hepatotoxic. The lesion was morphologically completely different from that produced by chlorpromazine [*42*], arsphenamine [*43*], nilevar [*44*] or methyltestosterone [*45*] in which the predominant feature is intrahepatic cholestasis without much liver cell damage [*46,47*]. All our patients presented a picture of massive or "submassive" necrosis with or without intrahepatic cholestasis. The pathology was similar to that produced by cinchophen and was indistinguishable from viral hepatitis.

THERAPY

All patients were kept at bedrest and given low fat diets with mixed vitamin supplements. Pyridoxine was used in three of our patients without any apparent improvement. Vitamin K preparations were ineffective. At the first sign of encephalopathy the intake of dietary protein was restricted and frequent enemas and neomycin were given. If the patient was unable to take oral medications, Chloromycetin® was administered parenterally. Transient clinical improvement was noted in each instance except in the week preceding death in Cases VIII and IX, in which coma was unresponsive to all therapy.

It is difficult to evaluate the effect of steroid therapy in our patients because of the various drugs and dosages to be considered. Symptomatic and chemical improvement occurred during the fourth week in five patients. Three of these did not receive steroids, one had received steroids for two weeks, and one had started steroid therapy two days previous to improvement. All three patients in whom signs of encephalopathy developed had received steroids before these signs were evident. At the time steroids were first given to these patients their symptoms were more severe than the other patients although the results of liver function

studies were not significantly different. The two patients who died received massive steroid therapy with only minor fluctuations in the degree of hepatic coma. In Case VI there appeared to be a shortening of the acute phase with the use of steroids and gamma globulin without any shortening of the total period of illness.

Significant fever occurred in only two patients. It was noted when steroids were discontinued despite persistence of significant hyperbilirubinemia. The fever lasted for four weeks in both patients, without altering the clinical course. In Case III administration of steroids was continued after the serum bilirubin levels had approached normal and no fever was noted.

All our patients had one or more of the criteria of severity of illness stated by Nelson [*48*] to be indications for the use of steroids. In no instance can steroids be credited with definitely shortening or lessening the severity of illness. Furthermore, administration of steroids did not prevent the appearance of encephalopathy and did not relieve it. If steroid administration was stopped prematurely a febrile reaction occurred.

PATHOGENESIS

The clinical and pathologic features of any one case of jaundice due to iproniazid administration are indistinguishable from those of viral hepatitis but when studied as a group the latter diagnosis does not appear tenable. There was no significant fever in our cases or in those of Zetzel and Kaplan [*35*]. The absence of fever in twelve consecutive cases of severe viral hepatitis would be unusual. In all cases jaundice was marked, with serum bilirubin levels of 25.0 mg. per cent or more. In a large series of infectious hepatitis [*50*] this serum bilirubin level was noted in only 2.7 per cent of the cases. In one epidemic in Denmark, a severe form of hepatitis was observed among older women [*51*], with a high percentage of fatalities [*52*]. If an epidemic of severe viral hepatitis were current at the time our cases were noted we would expect to have seen similar cases in patients who had not received iproniazid. This did not occur. Since seven patients received injections the possibility of introduction of homologous serum hepatitis exists but each patient received injections from a different private physician and in many instances too long before the onset of jaundice. Thus, although iproniazid cannot be unequivocally established as the etiologic agent in any single case, there is little doubt that it was the causative agent when the cases are studied as a group.

There appear to be two types of hepatotoxicity caused by iproniazid; direct toxic action and idiosyncrasy. The former was originally demonstrated in toxicity studies in rats and dogs [*17*], occurred with predictable frequency, and was dependent on dosage. Because of this, liver function tests were performed during the original clinical trials [*6,8,11,12*] but apparently showed only occasional transient abnormalities in patients receiving 2 to 10 mg./kg. daily of iproniazid. In six of these patients [*8*] and in one patient who had received 15 mg./kg. [*5*] autopsy was performed but only slight hepatic injury was noted; it was suggested [*53*] that if the dose of the drug were increased, more cases of hepatitis would occur. On the basis of the animal experiments it must be assumed that iproniazid is a true hepatic toxin or poison, at least in certain animal species.

The type of hepatotoxicity manifested by our patients is probably attributable to drug hypersensitivity. This is suggested by many factors. Jaundice has been observed in only a small percentage of those treated, 1.8 per cent of 268 patients in one series [*55*]. The total dosage and interval from the onset of therapy to the development of symptoms was variable. The jaundice occurred suddenly in the course of therapy. There is no correlation between the amount of drug given and the subsequent development of hepatic necrosis or of its severity. This is quite apparent if one compares the total dosage in our patients with the very much larger doses given to patients in whom overt jaundice did not subsequently develop [*56,57*]. The disease progresses after administration of the drug is stopped. The hepatic lesion, massive and "submassive" necrosis, has not been produced in experimental animals by iproniazid administration. There was no underlying liver disease, alcoholism or known dietary deficiency which might make these patients more susceptible to hepatotoxic substances. These factors, then, suggest an idiosyncrasy. Because of the known antienzymatic activity of iproniazid, it is intriguing to speculate about a possible trophopathic [*58*] action but evidence in this regard is lacking.

The shorter interval and smaller dosage required to cause liver damage in the patients who received two courses of therapy and the onset of

symptoms in Case II of Zetzel and Kaplan [*35*] following a single dose in the second course is suggestive of a hypersensitivity reaction. Other manifestations of hypersensitivity to iproniazid have been noted [*56*] but the hepatic cell damage in these cases is not an "allergy" in the usual sense. In our patients there was no history of preceding allergy. Only one patient had an urticarial lesion, late in the course of the illness. None of the usual manifestations of allergy were evident and there was no eosinophilia. It is important to emphasize that the clinical and pathological findings are distinct from those in allergic "cholangiolitis" [*59,60*].

As has been shown, the dose of iproniazid does not appear to be related to the onset of jaundice and the suggestion [*61*] that lowering the dose may lessen the danger does not appear to be valid. In view of the unpredictability of occurrence, rapidity of progression, and lack of relation to dosage, we are of the opinion that the use of iproniazid should be reserved for those few patients in whom the potential benefits from the drug are of such degree as to outweigh the possible development of severe hepatic necrosis with possible fatal outcome.

SUMMARY

1. Nine cases of jaundice associated with the administration of iproniazid, including two fatalities, are described, and the pertinent literature is reviewed.

2. All the patients were intensely jaundiced, with evidence of severe hepatic dysfunction indistinguishable clinically from viral hepatitis, except for the absence of fever. The prodromal period was short. Overt illness was prolonged, and full symptomatic recovery was delayed for many weeks, with indications of continuing hepatic abnormalities in some cases.

3. Laboratory examination indicated severe hepatocellular disease, although a "cholangiolitic" or obstructive phase was evident at the time of maximum icterus. One patient underwent exploratory laparotomy to exclude extrahepatic biliary tract obstruction.

4. Two autopsy and two biopsy specimens of liver were obtained. All showed massive and "submassive" necrosis indistinguishable from viral hepatitis. Early formation of septums and of regenerative nodules was noted, suggesting the possible subsequent development of postnecrotic cirrhosis.

5. There was no history of antecedent liver disease or allergy in these cases. In retrospective analysis, the occurrence of the hepatitis could not be predicted.

6. Hepatotoxicity in these cases apparently reflected idiosyncracy to iproniazid, unrelated to dosage.

Acknowledgment: We wish to thank Dr. Hans Popper for assistance in preparing the pathologic material. We are indebted to the many physicians of The Mount Sinai Hospital who allowed us to use their case material. We would like to thank Dr. Ezra Greenspan for assistance with the laboratory data.

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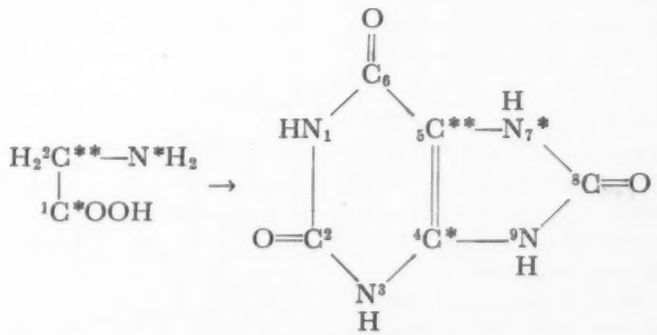
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Incorporation of Glycine-1-C^{14}, Glycine-2-C^{14} and Glycine-N^{15} into Uric Acid in Normal and Gouty Subjects*

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IN 1946 Sonne, Buchanan and Delluva [*1*] demonstrated that glycine is a specific precursor of uric acid in purine biosynthesis. They fed carboxyl-labeled glycine-C^{13} to pigeons, found a high concentration of isotope in carbon atom 4 of the excreted uric acid, and inferred that carbon atom 5 was derived from the α-carbon of glycine. In 1947 Shemin and Rittenberg [*2*] fed N^{15}-labeled glycine to a normal human subject and noted rapid incorporation of N^{15} into position 7 of the uric acid isolated from the urine. These and subsequent studies established the contribution of carbon-1, carbon-2 and the nitrogen of glycine to positions 4, 5 and 7, respectively, of the purine ring.

More recently Nemeth, Russell and Shemin [*5*] described another pathway of incorporation of the α-carbon of glycine into the purine ring, by way of the succinate-glycine cycle. The δ-carbon of δ-aminolevulinic acid, derived from the α-carbon of glycine, was found in pigeons to be incorporated into carbons 2 and 8 of the uric acid excreted. Significant incorporation into carbons 6 and 4 also was noted.



Glycine Uric Acid

The successive steps in the de novo synthesis of purines from glycine, 5-phosphoribosylamine, glutamine, aspartic acid, "active formate" and carbon dioxide, by way of glycinamide ribotide and subsequent intermediates of 4-amino-5-imidazole-carboxamide ribotide, have since been elucidated in publications notably by Buchanan [*3*] and Greenberg [*4*] and their respective associates.

These advances have made it possible, by use of isotope-labeled glycine and other uric acid precursors, to study more directly than

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This work was supported in part by a grant-in-aid (A-162) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and a grant from the Arthritis and Rheumatism Foundation, New York State Chapter.
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hitherto the nature of the presumptive derangement(s) of purine metabolism in gout. The initial experiments [*6,7*], using glycine-N^{15}, were conducted in two subjects with primary gout whose basal urinary uric acid excretion habitually was excessive while markedly elevated plasma uric acid levels were maintained; these subjects could be presumed to be overproducers of uric acid. Approximately threefold normal glycine-N^{15} incorporation into uric acid, by a rapid "shunt" pathway, was demonstrated in these patients. On the other hand, the rate and magnitude of glycine-N^{15} incorporation into uric acid were found to be indistinguishable from the normal in gouty subjects with hyperuricemia and essentially normal basal urinary uric acid excretion [*7–9*]. This latter group constitutes the majority of patients with primary gout.

In similar experiments with glycine-1-C^{14} administered in tracer doses to gouty subjects it was first reported [*10*] that greater than normal incorporation of C^{14} into uric acid occurred even in those patients in whom urinary uric acid excretion was not excessive, implying that by use of glycine-1-C^{14} overproduction of uric acid could be demonstrated in all gouty subjects. Subsequently, however, normal glycine-1-C^{14} incorporation curves were obtained in some patients with gout [*11,12*], a result in accord with the findings herein recorded.

The present studies deal with the incorporation of isotopic label from glycine-1-C^{14}, glycine-2-C^{14} and glycine-N^{15} into the urinary uric acid of gouty and non-gouty subjects. Experiments in which glycine-1-C^{14} or glycine-2-C^{14} was given concurrently with glycine-N^{15} also are recorded. The results reaffirm the inhomogeneity of the gouty population in respect to the utilization of glycine in the biosynthesis of uric acid. The metabolic aberrations underlying these dissimilarities, and the common bond of gout, are examined, with special reference to uric acid $\frac{N^{15}}{C^{14}}$ distribution ratios in double label experiments.

METHODS

Twenty-five isotope incorporation studies were made in twenty-three subjects, all males. Table 1 summarizes the pertinent descriptive data in these experimental subjects and indicates the isotopes and dosage administered.

Nine subjects had normal serum uric acid levels and no manifestations of gout; they were considered to be unequivocally non-gouty. Two subjects (C. R. and E. E.) had serum uric acid levels above the arbitrarily set upper limit of normal in males by the analytic method employed (6.5 mg. per cent) but had no indications of gout or family history of gout; they were provisionally classified as non-gouty. Two additional non-gouty patients (P. L. and J. G.) had hyperuricemia associated with overt renal disease and azotemia.

Ten subjects had unequivocal manifestations of gout. Five were classified as "normal excretors," five as "hyperexcretors." The distinction was made arbitrarily: "normal excretor" if the twenty-four-hour urinary uric acid excretion on a *basal* diet was less than 3 standard deviations above the normal mean basal urinary uric acid output (i.e., <628 mg./twenty-four hours, according to our data [*13*]), "hyperexcretor" if above this figure. In most cases a clear separation could be made on this basis but in some instances only a provisional classification was possible. Thus the basal urinary uric acid excretion in subjects P. C. and H. G., designated "hyperexcretors," was only slightly in excess of 628 mg./twenty-four hours. The classification of G. H. as a "normal excretor" also is uncertain. His basal urinary urate excretion was 616 ± 60 mg./twenty-four hours, which is high for a "normal excretor" although within our arbitrary definition. However, when the urinary uric acid excretion is calculated per kilogram body weight (128 kg.), the figure is quite within the limits of normal variation.

The prescribed diets, instituted at least five days before the isotope was administered, were uniformly low in purines but varied in protein and caloric intake according to individual requirements. The non-gouty subjects, who were convalescing from a variety of disorders, were variously allowed 70 to 100 gm. protein/day, as indicated by the data on urinary total nitrogen excretion. (Table 1.) The mean twenty-four-hour urinary uric acid excretion (558 mg.) therefore was substantially higher in these subjects than in a group of control subjects on a basal diet who were previously studied (418 mg./twenty-four hours) [*13*]. Some of the gouty subjects were maintained on a basal diet; others were permitted to continue on a diet including 4 ounces of meat. In the latter instances the basal urinary uric acid excretion had been previously estimated. (Table 1.) As a measure of control, the urinary total nitrogen excretion was determined daily during the period of study in each case. For estimation of the uric acid in urine and serum a modification of the method of Buchanan, Block and Christman was employed [*14*]. This method gives generally satisfactory correspondence with spectrophotometric analysis [*14*].

Isotope-labeled glycine was administered in a single oral dose: 100 mg./kg. body weight of glycine-N^{15} (N^{15} = 60.5 atom per cent excess), and/or

approximately 3 to 7 mg. of glycine-1-C^{14}* (25 to 60 mg./mc.) or glycine-2-C^{14}* (31 mg./mc.). The radioactivity administered ranged from 50 to 160 μc./dose. In some experiments glycine-1-C^{14} or glycine-2-C^{14} was given alone in the tracer dosages indicated, in others simultaneously with a glycine-N^{15} or glycine-N^{14} load. (Tables I and II.) The period of daily urine collections varied from one week to more than three weeks in individual cases.

The methods of synthesis of glycine-N^{15}, isolation and purification of the urinary uric acid, and measurement of N^{15} in a 60 degree mass spectrometer were the same as previously described [*15*]. In one case (A. R.) a sample of the urinary uric acid was degraded by the method of Sonne, Lin and Buchanan [*16*] to give the specific activity of N-7.

For estimation of C^{14} incorporation, samples of uric acid were recrystallized three times and dissolved in lithium carbonate to a final concentration of 4 mg. uric acid and 1.9 mg. lithium carbonate per ml. One ml. aliquots were dried in circular aluminum planchets, 1 inch in diameter, and assayed for radioactivity in a Nuclear windowless flow gas counter with a sensitivity of 0.85×10^6 C/M/μc. C^{14} above a background of 40 C/M under these conditions. Aliquots of administered doses were assayed under identical conditions in order to obviate the need for corrections for self-absorption. No differences in counting rate were observed when duplicate samples of glycine-C^{14} were diluted in solutions containing uric acid or glycine at the same concentration. However, radioactivity in dilute glycine-C^{14} solutions decreased markedly on standing at room temperature for several hours. Solutions containing 30 μg./ml. were stable for months when kept at 4°C.

RESULTS

The isotope incorporation data are presented in Table II and plotted in Figures 1 through 12. In contrast to the previous practice of expressing specific activities as atom per cent excess N^{15}, in the present study specific activities for N^{15} (as well as for C^{14}) are recorded as per cent of administered dose per gram uric acid. This method of presentation would seem to facilitate comparison of the experimental subjects, since glycine-N^{15} was administered at a dosage level of 100 mg./kg. body weight to subjects varying in weight from 60 to 104 kg., and the urinary uric acid excretion has not been demonstrated to be strictly proportional to body weight.

* Glycine-1-C^{14} and glycine-2-C^{14} were purchased from New England Nuclear Corp. Glycine-1-C^{14} was tested for purity by electrophoresis on paper at high voltage (40 volts/cm.). The radioactivity migrated as a single peak with added glycine, which separated well from alanine and serine.

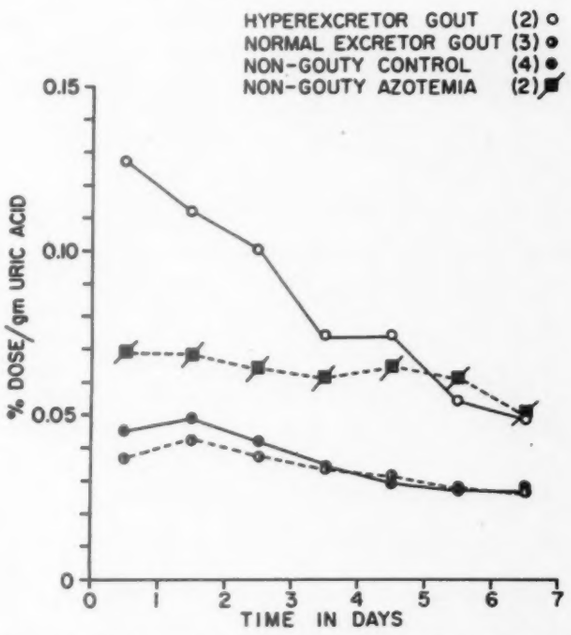


FIG. 1. Specific activity of uric acid-C^{14} (expressed as per cent dose/gm. uric acid) after administration of tracer doses of glycine-1-C^{14}. The curves are drawn through points representing mean values in two gouty "hyperexcretors," three gouty "normal excretors," four non-gouty subjects with normal renal function and two non-gouty subjects with azotemia.

Incorporation of Tracer Doses of Glycine-1-C^{14} into Uric Acid. Non-gouty control subjects (four experiments): The uric acid-C^{14} specific activities were usually maximal on the second day; if account is taken of the time required for absorption of the labeled glycine and the initial lag in synthesis of uric acid, it is probable that the highest specific activities were reached some time within the first twenty-four hours. By the seventh day the specific activities had fallen to levels averaging 50 to 60 per cent of the peak values. (Table II, Fig. 1.) The cumulative excretion of uric acid-C^{14} averaged 0.143 per cent of the dose for the first seven days but continued to increase significantly over the next two weeks. (Fig. 2.)

"Normal excretor" gouty patients (three experiments): No significant differences in the pattern or magnitude of C^{14} incorporation into uric acid were observed between this group and the non-gouty control subjects. (Figs. 1 and 2, Table II.) The mean cumulative uric acid-C^{14} excretion of the group fell somewhat below that of the control subjects (Fig. 2) because of the very low urinary output of uric acid in subject L. W. (Table I.)

TABLE I

DESCRIPTIVE DATA AND CLASSIFICATION OF THE TWENTY-THREE SUBJECTS STUDIED

No.	Subject, Age (yr.), Weight (kg.)	Uric Acid		Serum Non-protein Nitrogen (Blood Urea Nitrogen) (mg. %)	Urinary Total Nitrogen (gm./24 hr.)	Clinical Status	Isotope Administered
		Serum (mg. %)	Urine* (mg./24 hr. ± S.D.)				
			Non-gouty Patients with Normal Renal Function				
1.	B. K., 48, 71	4.7	555 ± 28	28	11.3	Angina pectoris	Glycine-1-C^{14}, tracer dose
2.	M. M., 28, 50	4.9	644 ± 50	(12)	8.4	Benign paroxysmal peritonitis (remission)	Glycine-1-C^{14}, tracer dose
3.	T. R., 35, 55	5.4	480 ± 35	28	9.8	Schistosomiasis, treated	Glycine-1-C^{14}, tracer dose
4.	J. M., 60, 83	5.4	600 ± 46	....	....	.....	Glycine-1-C^{14}, tracer dose
5.	L. C., 28, 76	5.7	482 ± 55	(8)	11.9	Duodenal ulcer, treated	Glycine-1-C^{14} + glycine-N^{15} 100 mg./kg.
6.	T. G., 21, 60	4.2	528 ± 52	26	10.5	Spontaneous pneumothorax, convalescent	Glycine-1-C^{14} + glycine-N^{15} 100 mg./kg.
7.	L. J., 64, 79	.....	680 ± 62	....	....	Aplastic anemia, transfused	Glycine-1-C^{14} + glycine-N^{14} 100 mg./kg.
8.	T. M., 38, 93	4.8	637 ± 81	(11)	13.5	Spontaneous pneumothorax, convalescent	Gycine-1-C^{14} + glycine N^{14} 50 mg./kg.
9.	L. Y., 37, 63	5.8	444 ± 88	(11)	11.1	Schistosomiasis, treated	Glycine-2-C^{14}, tracer dose
10.	C. R., 22, 82	7.2–7.9†	643 ± 50	(15)	14.5	Spontaneous pneumothorax, convalescent; no history of acute gouty arthritis	Glycine-2-C^{14}, tracer dose
11.	E. E., 52, 56	7.0–7.5†	450 ± 28	36	11.0	Myocardial infarction, convalescent; no history of acute gouty arthritis	Glycine-2-C^{14}, tracer dose
			Non-gouty Patients with Azotemia				
12.	P. L., 69, 68	8.4–6.7	577 ± 44	68–46	10.1	Hypertensive cardiovascular disease, nephrosclerosis, pyelonephritis	Glycine-1-C^{14}, tracer dose
13.	J. G., 55, 73	9.0	285 ± 34	81	8.1	Chronic pyelonephritis, hypertension	Glycine-1-C^{14}, tracer dose
			Gouty Patients, "Normal Excretors"				
14.	I. S., 54, 83	10.0	609 ± 76 (383)	39	13.4	Recurrent gouty arthritis 11 years, non-tophaceous, normal renal status	Glycine-1-C^{14}, tracer dose
15.	L. O., 41, 77	10.6	617 ± 87 (368)	35	11.1	Recurrent gouty arthritis 10 years, non-tophaceous, normal renal status	Glycine-1-C^{14}, tracer dose
16.	L. W., 49, 77	7.4	(253 ± 19)	(12)	7.7	Recurrent gouty arthritis 10 years, non-tophaceous, normal renal status	Glycine-1-C^{14}, tracer dose
17A.	A. R., 47, 86	9.0	640 ± 64 (450)	33	....	Recurrent gouty arthritis 14 years, non-tophaceous, normal renal status	Nov. 1956: Glycine-1-C^{14} + glycine-N^{15}, 100 mg./kg.
17B.	A. R., 48, 89	9.0	624 ± 70 (380)	....	13.5	.....	Mar. 1958: Glycine-2-C^{14} + glycine-N^{15}, 100 mg./kg.
18.	G. H., 47, 128	12.0	752 ± 87 (616)	28	13.1	Recurrent gouty arthritis 23 years, non-tophaceous, normal renal status	Glycine-2-C^{14}, tracer dose
			Gouty Patients, "Hyperexcretors"				
19.	D. R., 41, 96	10.3	1200 ± 62 (689)	31	....	Recurrent gouty arthritis 13 years, repeated renal colic and urate calculi, progressive tophaceous deposits for 4 years, renal status remains normal	Glycine-1-C^{14}, tracer dose
20A.	H. G., 44, 104	10.5	(684 ± 87)	34	8.9	Recurrent gouty arthritis 20 years, early tophaceous deposits, normal renal status	Jan. 1957: Glycine-1-C^{14} + glycine-N^{15}, 100 mg./kg.
20B.	H. G., 45, 103	11.0	745 ± 51	34	11.6		Jan. 1958: Glycine-1-C^{14}, tracer dose
21.	C. W., 33, 98	10.0	1140 (1070)	35	14.6	Recurrent gouty arthritis 2 years, non-tophaceous, normal renal status	Glycine-1-C^{14} + glycine-N^{15}, 100 mg./kg.
22.	P. C., 61, 70	9.5	(634 ± 57)	33	9.4	Recurrent gouty arthritis 36 years, progressive tophaceous deposits 25 years, uricosuric therapy 1951–1957; tophi practically disappeared; renal status fair	Glycine-2-C^{14} + glycine-N^{15}, 100 mg./kg.
23.	S. R., 40, 84	12.2	1058 ± 131 (890)	27	11.1	Recurrent gouty arthritis 10 years, non-tophaceous, normal renal status	Glycine-2-C^{14} + glycine-N^{15}, 100 mg./kg.

* Figures in parentheses represent the daily urinary uric acid excretion on a basal diet. The figures not in parentheses represent the daily urinary uric acid excretion on more liberal diets (note daily urinary total nitrogen excretion). The reasons for the provisional classification of G. H. as "normal excretor" and H. G. and P. C. as "hyperexcretors" are discussed in the text.

† These patients with unexplained hyperuricemia are provisionally classified as non-gouty (see text).

"Hyperexcretor" gouty patients (two experiments): Subjects H. G. and D. R. showed specific activities approximately two times and three and a half times, respectively, as high as the non-gouty subjects and "normal excretor" gouty patients. (Table II, Fig. 1.) The specific activity in D. R. fell sharply, reaching a level by the seventh day of only 24 per cent of the peak value on the first day. Because of the high uric acid excretion in H. G. and D. R. the cumulative

TABLE IIA

INCORPORATION OF TRACER DOSES OF GLYCINE-1-C^{14} AND GLYCINE-2-C^{14} INTO URINARY URIC ACID IN NON-GOUTY AND GOUTY SUBJECTS; FIRST SEVEN DAYS

(Results expressed as per cent dose/gm. uric acid; in parentheses, as per cent dose)

No.	Subject	Isotope	Day						
			1	2	3	4	5	6	7
Non-gouty Patients with Normal Renal Function									
1.	B. K.	Glycine-1-C^{14}	0.041 (0.021)	0.047 (0.024)	0.048 (0.027)	0.043 (0.025)	0.040 (0.024)	0.038 (0.022)	0.036 (0.021)
2.	M. M.	Glycine-1-C^{14}	0.047 (0.030)	0.049 (0.030)	0.032 (0.022)	0.028 (0.019)	0.020 (0.012)	0.019 (0.011)	0.017 (0.010)
3.	T. R.	Glycine-1-C^{14}	0.046 (0.021)	0.049 (0.020)	0.042 (0.019)	0.031 (0.016)	0.026 (0.016)	0.023 (0.011)	0.021 (0.010)
4.	J. M.	Glycine-1-C^{14}	....	0.050 (0.028)	0.047 (0.030)	....	....	0.029 (0.019)	0.028 (0.017)
9.	L. Y.	Glycine-2-C^{14}	0.172 (0.058)	0.118 (0.046)	0.089 (0.045)	0.108 (0.052)	0.070 (0.026)	....	0.053 (0.031)
10.	C. R.	Glycine-2-C^{14}	0.037 (0.024)	0.057 (0.037)	....	0.046 (0.035)	0.042 (0.025)	0.034 (0.020)	0.037 (0.022)
11.	E. E.	Glycine-2-C^{14}	0.111 (0.053)	0.096 (0.047)	0.102 (0.047)	0.085 (0.037)	0.078 (0.036)	0.066 (0.028)	0.082 (0.033)
Non-gouty Patients with Azotemia									
12.	P. L.	Glycine-1-C^{14}	0.070 (0.033)	0.053 (0.031)	0.053 (0.033)	0.051 (0.030)	0.056 (0.033)	0.048 (0.028)	0.036 (0.022)
13.	J. G.	Glycine-1-C^{14}	0.067 (0.022)	0.083 (0.024)	0.074 (0.025)	0.070 (0.024)	0.072 (0.020)	0.074 (0.017)	0.063 (0.015)
Gouty Patients, "Normal Excretors"									
14.	I. S.	Glycine-1-C^{14}	0.035 (0.027)	0.037 (0.026)	0.035 (0.020)	0.033 (0.019)	0.031 (0.014)	0.028 (0.017)	0.022 (0.012)
15.	L. O.	Glycine-1-C^{14}	0.042 (0.026)	0.042 (0.032)	0.037 (0.026)	0.033 (0.020)	0.029 (0.017)	0.025 (0.015)	0.027 (0.016)
16.	L. W.	Glycine-1-C^{14}	0.034 (0.0086)	0.046 (0.013)	0.040 (0.010)	0.034 (0.0081)	0.033 (0.0088)	0.031 (0.0074)	0.029 (0.0069)
18.	G. H.	Glycine-2-C^{14}	0.034 (0.025)	0.040 (0.030)	0.050 (0.032)	0.040 (0.026)	0.037 (0.033)	0.031 (0.023)	0.024 (0.020)
Gouty Patients, "Hyperexcretors"									
19.	D. R.	Glycine-1-C^{14}	0.168 (0.200)	0.126 (0.154)	0.103 (0.123)	0.071 (0.0845)	0.062 (0.071)	0.044 (0.058)	0.040 (0.043)
20B.	H. G.	Glycine-1-C^{14}	0.086 (0.067)	0.099 (0.081)	0.096 (0.068)	0.076 (0.053)	0.085 (0.067)	0.063 (0.048)	0.056 (0.037)

uric acid-C^{14} excretion during the first day exceeded the average normal level threefold and eightfold, respectively. (Table I, Fig. 2.)

Non-gouty azotemic patients (two experiments): Subjects P. L. and J. G. with hyperuricemia due to intrinsic renal disease but without history or evidence of gout exhibited higher specific activities than did any of the non-gouty or "normal excretor" gouty subjects and thus occupied a position intermediate between the latter group and the gouty "hyperexcretors." (Fig. 1.) However, the cumulative uric acid-C^{14}

TABLE IIB

INCORPORATION OF GLYCINE-1-C^{14} AND GLYCINE-2-C^{14} GIVEN WITH (LOAD) DOSES OF GLYCINE-N^{15} OR GLYCINE-N^{14} IN NON-GOUTY AND GOUTY SUBJECTS; FIRST SEVEN DAYS

(Results expressed as per cent dose/gm. uric acid; in parentheses as per cent dose; in roman, C^{14} incorporation; in italics, N^{15} incorporation)

No.	Subject	Isotope	Day						
			1	2	3	4	5	6	7
		Non-gouty Patients with Normal Renal Function							
5.	L. C.	Glycine-1-C^{14}	0.016	0.024	0.027	0.025	0.027	0.024	0.020
		+	(0.0094)	(0.010)	(0.012)	(0.013)	(0.011)	(0.012)	(0.0097)
		Glycine N^{15}	*0.025*	*0.060*	*0.052*	*0.041*	*0.044*	*0.040*	*0.040*
		100 mg./kg.	(*0.016*)	(*0.026*)	(*0.024*)	(*0.022*)	(*0.018*)	(*0.021*)	(*0.019*)
6.	T. G.	Glycine-1-C^{14}	0.016	0.020	0.017	0.021	0.017	0.018	0.019
		+	(0.0080)	(0.0098)	(0.011)	(0.011)	(0.011)	(0.0097)	(0.0092)
		Glycine N^{15}	*0.024*	*0.033*	*0.031*	*0.024*	*0.029*	*0.029*	*0.033*
		100 mg./kg.	(*0.012*)	(*0.016*)	(*0.019*)	(*0.013*)	(*0.018*)	(*0.015*)	(*0.016*)
7.	L. J.	Glycine-1-C^{14}	.....	.....	0.025	0.028	0.0059	0.022	0.016
		+	.....	.....	(0.018)	(0.016)	(0.0044)	(0.014)	(0.011)
		Glycine N^{14}	.....	.....	.....	.....	.....	.....	.....
		100 mg./kg.	.....	.....	.....	.....	.....	.....	.....
8.	T. M.	Glycine-1-C^{14}	0.018	0.021	0.020	0.022	0.014	0.014	0.013
		+	(0.0081)	(0.013)	(0.014)	(0.013)	(0.0089)	(0.0076)	(0.0081)
		Glycine N^{14}	.....	.....	.....	.....	.....	.....	.....
		50 mg./kg.	.....	.....	.....	.....	.....	.....	.....
		Gouty Patients, "Normal Excretors"							
17A.	A. R.	Glycine-1-C^{14}	0.013	0.015	0.015	0.017	0.016	0.013	0.013
		+	(0.010)	(0.0093)	(0.0097)	(0.0096)	(0.010)	(0.0094)	(0.0083)
		Glycine N^{15}	*0.023*	*0.030*	*0.034*	*0.033*	*0.032*	*0.028*	*0.028*
		100 mg./kg.	(*0.019*)	(*0.019*)	(*0.022*)	(*0.018*)	(*0.021*)	(*0.020*)	(*0.017*)
17B.	A. R.	Glycine-2-C^{14}	0.016	0.025	0.026	0.021	0.025	0.020	0.019
		+	(0.011)	(0.013)	(0.015)	(0.015)	(0.017)	(0.014)	(0.011)
		Glycine N^{15}	*0.023*	*0.025*	*0.036*	*0.030*	*0.030*	*0.029*	*0.026*
		100 mg./kg.	(*0.025*)	(*0.013*)	(*0.021*)	(*0.021*)	(*0.021*)	(*0.020*)	(*0.014*)
		Gouty Patients, "Hyperexcretors"							
20A.	H. G.	Glycine-1-C^{14}	0.027	0.035	0.035	0.029	0.029	0.025	0.021
		+	(0.018)	(0.022)	(0.022)	(0.018)	(0.022)	(0.023)	(0.016)
		Glycine N^{15}	*0.062*	*0.085*	*0.085*	*0.077*	*0.070*	*0.059*	*0.053*
		100 mg./kg.	(*0.042*)	(*0.054*)	(*0.054*)	(*0.049*)	(*0.053*)	(*0.056*)	(*0.039*)
21.	C. W.	Glycine-1-C^{14}	0.025	0.028	0.021	0.018	0.017	0.014	0.012
		+	(0.032)	(0.028)	(0.023)	(0.018)	(0.016)	(0.011)	(0.011)
		Glycine N^{15}	*0.044*	*0.067*	*0.059*	*0.051*	*0.048*	*0.041*	*0.037*
		100 mg./kg.	(*0.056*)	(*0.068*)	(*0.065*)	(*0.051*)	(*0.046*)	(*0.034*)	(*0.032*)
22.	P. C.	Glycine-2-C^{14}	0.066	0.085	0.073	0.064	0.052	0.076	0.039
		+	(0.036)	(0.059)	(0.047)	(0.036)	(0.035)	(0.044)	(0.026)
		Glycine N^{15}	*0.107*	*0.113*	*0.102*	*0.091*	*0.087*	*0.082*	*0.079*
		100 mg./kg.	(*0.059*)	(*0.079*)	(*0.066*)	(*0.051*)	(*0.058*)	(*0.047*)	(*0.053*)
23.	S. R.	Glycine-2-C^{14}	0.104	0.098	0.080	0.075	0.052	0.044	.....
		+	(0.101)	(0.105)	(0.084)	(0.078)	(0.062)	(0.056)	.....
		Glycine N^{14}	.....	.....	.....	.....	.....	.....	.....
		100 mg./kg.	.....	.....	.....	.....	.....	.....	.....

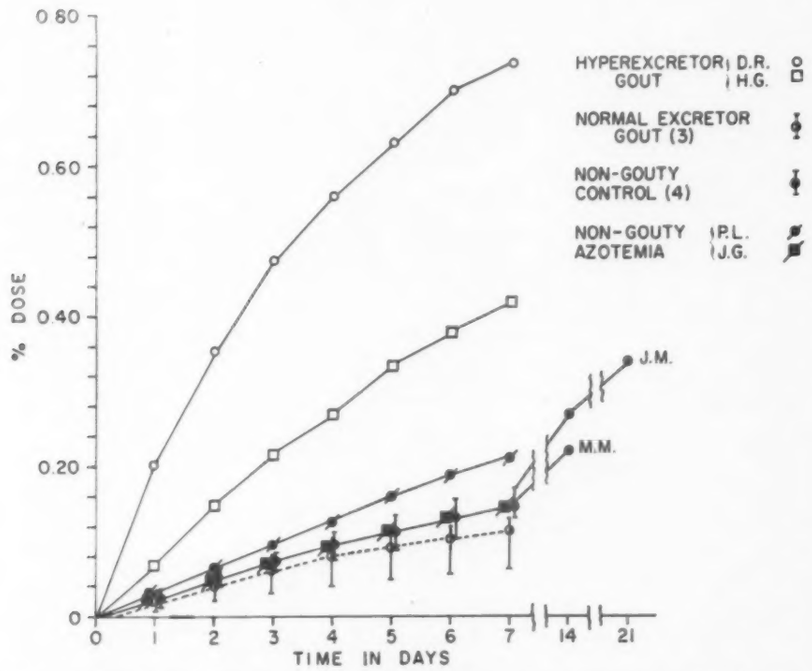


FIG. 2. Cumulative excretion of uric acid-C^{14} (expressed as per cent dose) after administration of tracer doses of glycine-1-C^{14}. The subjects are the same as in Figure 1.

excretion was not greater than normal in the subject (J. G.) with an abnormally low urinary uric acid excretion. (Fig. 2.)

Incorporation of Tracer Doses of Glycine-2-C^{14} into Uric Acid. Non-gouty control subjects (three experiments): Considerable variation in the specific activities (Fig. 3) was observed in this group (C. R., E. E., L. Y.) but the peak values (0.057, 0.111 and 0.172 per cent dose/gm. uric acid) were all greater than the highest value (0.050 per cent dose/gm.) obtained in control subjects receiving tracer doses of glycine-1-C^{14}. The peak specific activity was attained on the first day in two of the subjects and on the second day in the third subject. Cumulative glycine-2-C^{14} excretion in uric acid (Fig. 4) was less variable than the specific activity in this group after the first day, and was one and a half to two times as great as the cumulative uric acid-C^{14} excretion in control subjects who received tracer glycine-1-C^{14}.

Gouty patient ("normal excretor"): The uncertainty in classifying G. H. as a "normal excretor" has already been mentioned. In any event his uric acid-C^{14} excretion (specific activity and cumulative excretion) was lower than observed in the control subjects receiving tracer doses of glycine-2-C^{14}. (Figs. 3 and 4.)

Incorporation into Uric Acid of Glycine-1-C^{14}

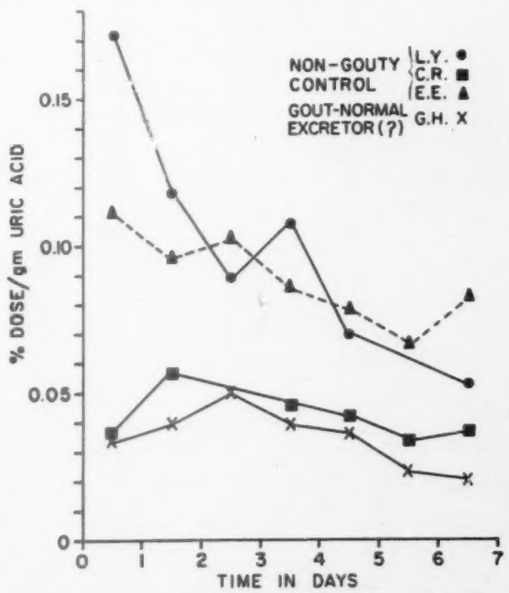


FIG. 3. Specific activity of uric acid-C^{14} after administration of tracer doses of glycine-2-C^{14} in three non-gouty subjects and one gouty "normal excretor."

Administered with Loading Doses of Glycine (Figs. 5 and 6). Non-gouty control subjects (four experi-*

* All subjects received 100 mg. glycine/kg. body weight with the exception of T. M. who received only 50 mg./kg. The results in T. M. were not significantly different from those in other control subjects.

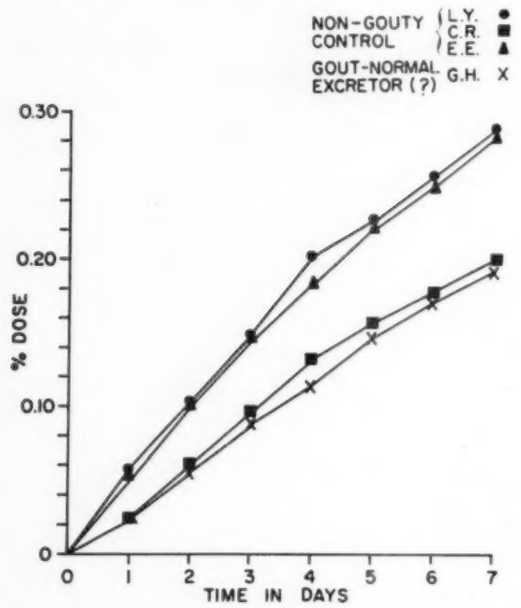


FIG. 4. Cumulative excretion of uric acid-C^{14} after administration of tracer doses of glycine-2-C^{14}. The subjects are the same as in Figure 3.

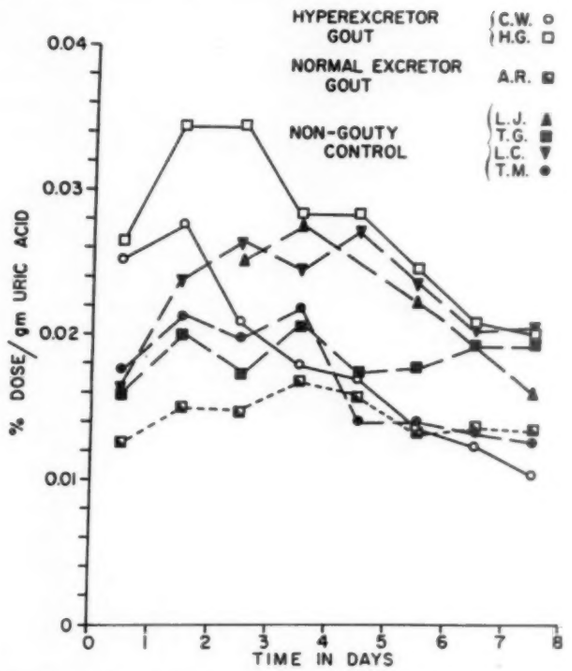


FIG. 5. Specific activity of uric acid-C^{14} after administration of glycine-1-C^{14}, with a glycine load, in two gouty "hyperexcretors," one gouty "normal excretor" and four non-gouty subjects.

ments): Peak specific activities averaged somewhat less than half of those obtained in control subjects receiving tracer doses of glycine-1-C^{14}. The mean ratio, uric acid-$C^{14}_{(tracer)}$/uric acid-$C^{14}_{(load)}$ was 2.2 for the first three days. Similar observations were previously recorded by Wyngaarden [*10*] in two "normal excretor" gouty subjects but the tracer/load ratios reported approximated 10.

The rate of C^{14} incorporation usually fell off less rapidly than when tracer doses were administered. Consequently the cumulative excretion of C^{14}-labeled uric acid over the first seven days was about half of that obtained with tracer doses.

"Normal excretor" gouty patient (one experiment): The peak specific activity in this patient (A. R.) was lower than in any of the control subjects and there was little daily variation during the first week.

"Hyperexcretor" gouty patients (two experiments): In contrast to the results obtained with tracer doses of glycine-1-C^{14} and with loading doses of glycine-N^{15}, to be presented subsequently, the peak specific activities of C^{14} in the two "hyperexcretor" gouty patients (H. G. and C. W.) in this experiment were not strikingly higher than those observed in some of the non-gouty subjects, and in C. W. might even be considered to be within the normal range. However, in both H. G. and C. W. the specific activities during the first two days were higher than those observed in the other subjects and the cumulative total uric acid-C^{14} excretion was markedly increased in both instances. (Fig. 6.)*

The results in H. G. of glycine-1-C^{14} administration simultaneously with a glycine load may be compared directly with those obtained when this patient received *tracer* glycine-1-C^{14} under similar dietary conditions. The peak specific activity after the tracer dose was 0.099 per cent dose/gm. uric acid whereas after the loading dose it was 0.035 per cent dose/gm. The seven-day cumulative excretion of uric acid-C^{14} was 0.421 per cent following the tracer dose and this was reduced to 0.140 per cent after the loading dose.

Incorporation into Uric Acid of Glycine-2-C^{14} Administered with Loading Doses of Glycine, 100

* It should be noted that one "hyperexcretor" gouty patient (H. G.) was on a meat-free regimen during this study whereas the non-gouty subjects and the "normal excretor" gouty patient were taking a more liberal diet. The urine of patient C. W. was quite acid and spontaneous precipitation of uric acid in the twenty-four hour urine collections after the first three days was noted. For this reason the figures for cumulative uric acid-C^{14} excretion after the third day represent only minimal estimates.

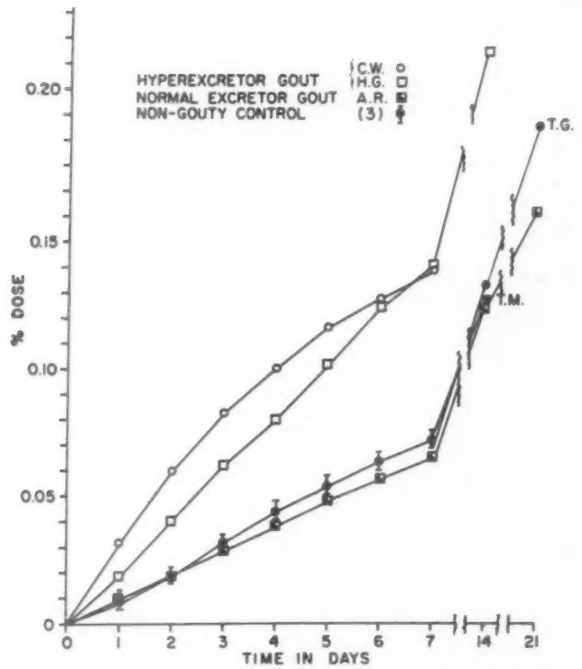


FIG. 6. Cumulative excretion of uric acid-C^{14} after administration of glycine-1-C^{14} with a glycine load. The subjects are the same as in Figure 5.

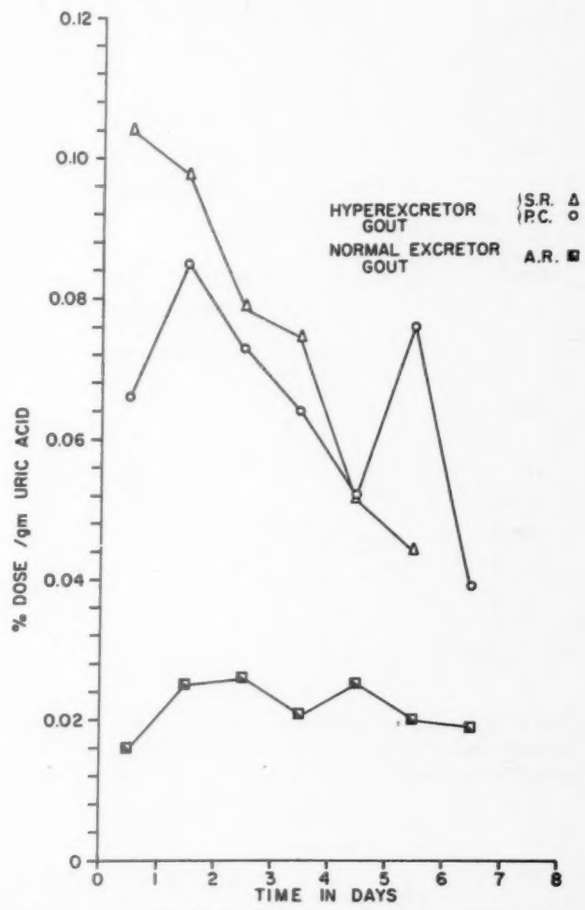


FIG. 7. Specific activity of uric acid-C^{14} after administration of glycine-2-C^{14}, with a glycine load, in two gouty "hyperexcretors" and one gouty "normal excretor."

mg./kg. Body Weight (*Figs. 7 and 8*). *"Normal excretor" gouty patient* (*one experiment*): The results of this experiment are to be compared with those obtained in the same patient (A. R.) given glycine-1-C^{14} with 100 mg. glycine/kg. body weight under similar experimental conditions one and a half years previously. Incorporation of glycine-2-C^{14} into uric acid (Figs. 7 and 8, Table II) was significantly greater than that of glycine-1-C^{14} (Figs. 5 and 6, Table II) although, as will be described, the incorporation of glycine-N^{15} was essentially the same on both occasions. The seven-day cumulative urinary uric acid-C^{14} excretion ratio, $-2\text{-}C^{14}{}_{(load)}/-1\text{-}C^{14}{}_{(load)}$, was 1.36. However, glycine-2-C^{14} incorporation under these load conditions was considerably less than the incorporation of *tracer* doses of glycine-2-C^{14} in a "normal excretor" gouty patient (G. H.) and control subjects. (*Cf.* Figs. 7 and 8 with Figs. 3 and 4.)

"Hyperexcretor" gouty patients (*two experiments*): In both subjects (S. R., P. C.) glycine-2-C^{14} incorporation (Figs. 7 and 8) was considerably greater than the glycine-1-C^{14} incorporation in two other "hyperexcretor" gouty patients (C. W., H. G.) under similar load conditions. (Figs. 5 and 6.)

Incorporation into Uric Acid of Glycine-N^{15} (*100 mg./kg. Body Weight*) (*Figs. 9 and 10*). In all experiments in this group glycine-N^{15} was mixed together with glycine-1-C^{14} or glycine-2-C^{14} and the mixture was given as a single dose so that the respective incorporation of isotopes could be compared directly.

Non-gouty control subjects (*two experiments*): In earlier studies the specific activity of uric acid-N^{15} in non-gouty subjects and "normal excretor" gouty patients was observed generally to increase significantly from day 1 to day 2 and occasionally even to day 3 before reaching a plateau, which was maintained throughout the first week [*6,7*]. Similar patterns were exhibited by subject D. F. in the report of Bishop et al. [*9*]. In the present study the same trend is evident in L. C. and T. G. (Figs. 9 and 10) although the curve in L. C. falls off rather sharply, thus resembling that seen in gouty "hyperexcretors." Because of the aberrant N^{15}/C^{14} ratios in L. C.

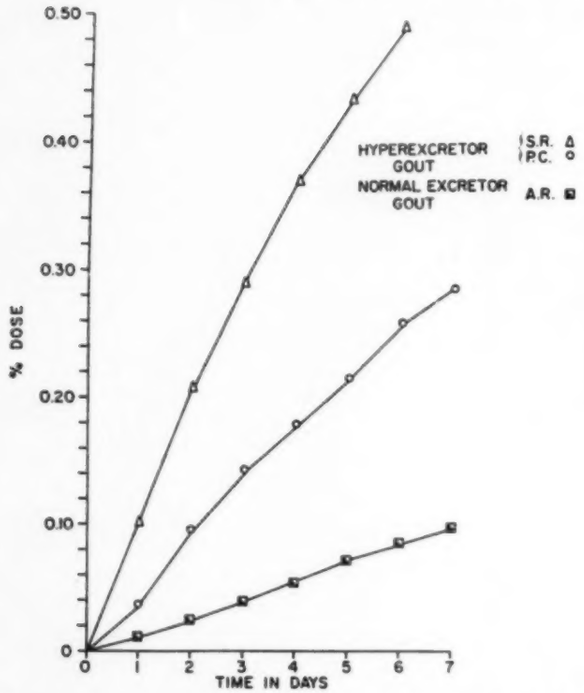


FIG. 8. Cumulative excretion of uric acid-C^{14} after administration of glycine-2-C^{14} with a glycine load. The subjects are the same as in Figure 7.

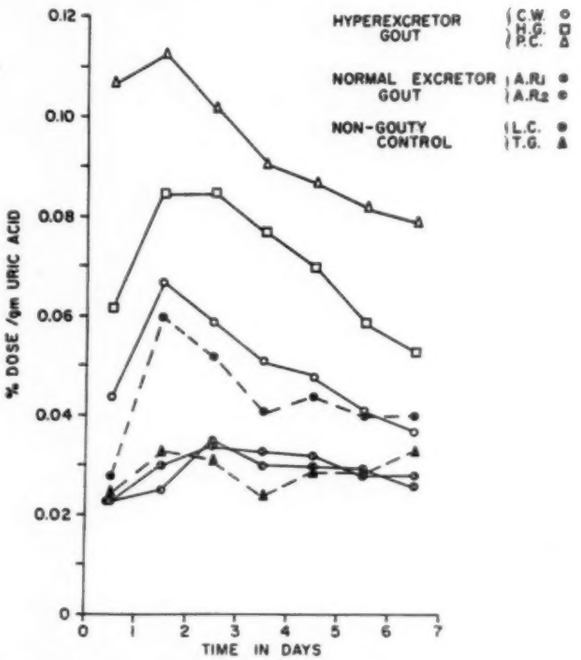


FIG. 9. Specific activity of uric acid-N^{15} after administration of glycine-N^{15}, 100 mg./kg. body weight, in three gouty "hyperexcretors," one gouty "normal excretor," and two non-gouty subjects. Two experiments in A. R., at an interval of one and a half years, are represented.

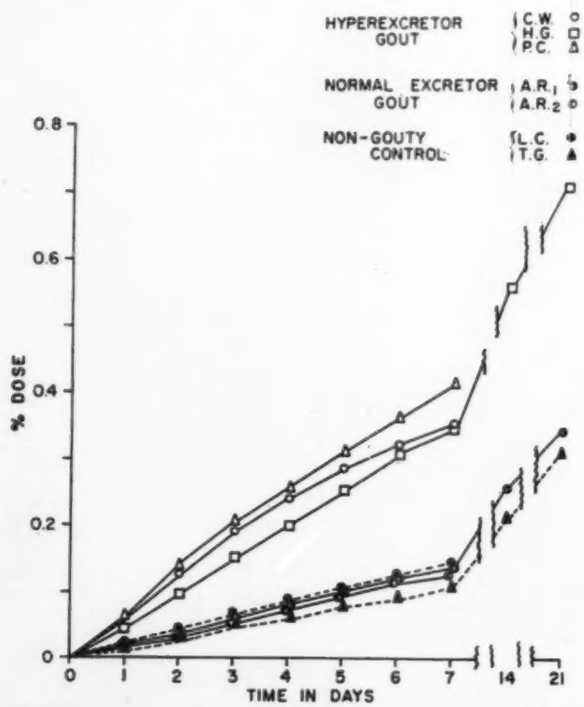


FIG. 10. Cumulative excretion of uric acid-N^{15} after administration of glycine-N^{15}, 100 mg./kg. body weight. The subjects are the same as in Figure 9.

on the second and third days it is believed that these points may be spuriously high.

"Normal excretor" gouty patient (two experiments in one patient): The curves obtained in both studies on this patient (A. R.) at an interval of a year and a half were in a good agreement. (Figs. 9 and 10.) The uric acid-N^{15} excretion curve was similar to that observed in control subject T. G. and in control subjects of previous studies [*6,7*].

"Hyperexcretor" gouty patients (three experiments): As previously observed in "hyperexcretor" gouty patients [*6,7*], the peak specific activity on the second day was about three or more times the normal level; within a week the specific activity fell significantly. (Fig. 9.) However, the peak specific activity in C. W. was not as high as in the other "hyperexcretor" gouty subjects studied.

Uric acid N^{15}:C^{14} Ratios in Double Label Experiments (Figs. 11 and 12). The data obtained by concurrent oral administration of glycine-N^{15} and glycine-C^{14} permit calculation of the relative N^{15}:C^{14} incorporation into uric acid. The ratios so procured suggest additional differences between non-gouty and "hyperexcretor" gouty subjects on the one hand, and perhaps between

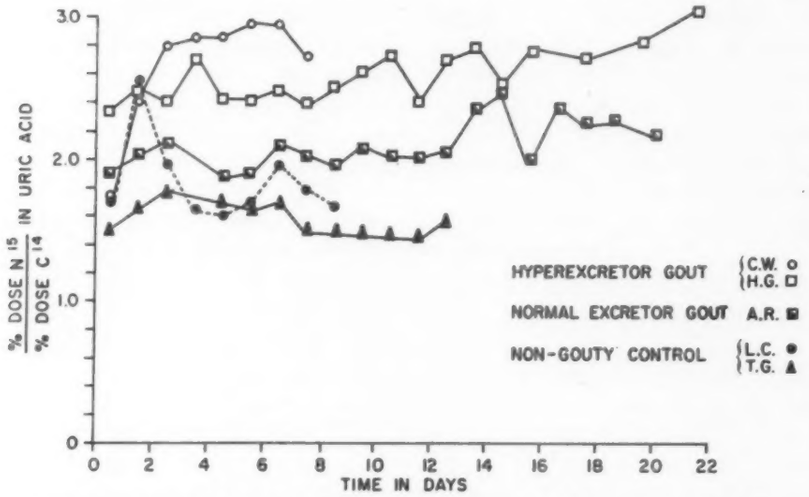


FIG. 11. Uric acid N^{15}/C^{14} ratios after administration of glycine-N^{15} and glycine-1-C-^{14} in two gouty "hyperexcretors," one gouty "normal excretor" and two non-gouty subjects.

"normal excretor" and non-gouty subjects on the other.

N^{15} incorporation consistently was in great excess of -1-C^{14} incorporation (Fig. 11) and somewhat in excess of -2-C^{14} incorporation. (Fig. 12.) The differences in these ratios are consonant with the generally greater incorporation of -2-C^{14} than of -1-C^{14}.

The N^{15}/-1-C^{14} ratios ranged from about 1.7 to 1.8 in control subjects to 2.4 to 2.8 in the gouty "hyperexcretors." The single "normal excretor" gouty patient for whom ratios are available gave an intermediate value at about 2. In contrast, the N^{15}/-2-C^{14} ratios in the "hyperexcretor" gouty patient studied were not significantly higher than the average 1.4 ratio in the "normal excretor" gouty patient.

The N^{15}/C^{14} ratios exceed those to be expected if glycine were incorporated into uric acid solely as intact glycine. To determine whether or not the high N^{15}/-1-C^{14} ratios could be quantitatively explained by localization of N^{15} into positions other than accounted for by incorporation as intact glycine (i.e., other than position 7), the urinary uric acid in A. R., a "normal excretor" gouty patient given both glycine-1-C^{14} and glycine-N^{15}, was degraded to permit separate assay of N^{15}-7 and N^{15}-(1 + 3 + 9). The results, summarized in Table III, indicate that a substantial proportion of the total uric acid-N^{15} was present in positions other than N-7, even on the first day or two after administration of glycine-N^{15}. Table III also gives the ratios, N^{15}-7/total C^{14}. As will be

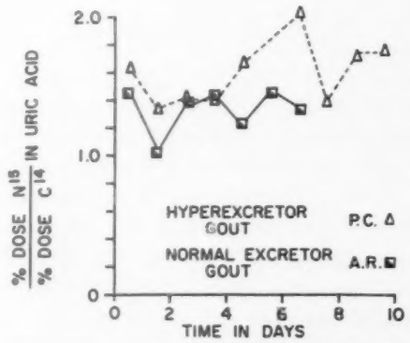


FIG. 12. Uric acid N^{15}/C^{14} ratios after administration of glycine-N^{15} and glycine-2-C^{14} in one gouty "hyperexcretor" and one gouty "normal excretor."

noted, the ratios are all significantly greater than 1.0. (If some of the uric acid-C^{14} were in positions other than C-4, as is altogether likely, the ratios, N^{15}-7/C^{14}-4, would be even higher than those shown for N^{15}-7/total C^{14}). The significance of these findings will be discussed subsequently.

COMMENTS

The Inhomogeneity of Patients with Primary Gout in Respect to the Utilization of Glycine in the Biosynthesis of Uric Acid. The data of the present study substantiate and amplify previous reports [*6–9,11*] indicating that, within the category of primary gout, there are significant differences among patients with respect to the rate and magnitude of glycine incorporation into uric acid. These dissimilarities, first shown with glycine-N^{15} [7], are demonstrated in the present study to be apparent also with glycine-1-C^{14},

TABLE III

DISTRIBUTION OF ATOM PER CENT EXCESS N^{15} IN URIC ACID OF "NORMAL EXCRETOR" GOUTY SUBJECT, A. R.

Day	N^{15}-7	N^{15}-(1 + 3 + 9)	Total N^{15}		Per cent $\frac{N^{15}\text{-}7}{\text{Total } N^{15}}$		$\frac{N^{15}\text{-}7}{\text{Total } C^{14}}$	
			Calculated from Degraded Uric Acid	Determined from Intact Uric Acid	Calculated from Degraded Uric Acid	Determined from Intact Uric Acid	A*	B*
1.	0.205	0.043	0.0835	0.069	61.5	74.5	1.18	1.41
2.	0.218	0.048	0.0905	0.092	60.5	59.2	1.24	1.21
3.	0.223	0.051	0.094	0.103	59.3	54.1	1.34	1.23
7.	0.205	0.053	0.091	0.086	53.7	59.6	1.10	1.22
15.	0.162	0.046	0.075	0.074	54.0	54.8	1.33	1.34

* The ratios under (A) were obtained by multiplying $\frac{N^{15}}{C^{14}}$ ratios (Table IIB) by per cent total excess $\frac{N^{15}\text{-}7}{\text{total } N^{15}}$ as calculated from degraded uric acid. The ratios under (B) were obtained by multiplying $\frac{N^{15}}{C^{14}}$ ratios by per cent total excess $\frac{N^{15}\text{-}7}{\text{total } N^{15}}$ as determined from intact uric acid.

whether given in tracer doses or, although less conspicuously, with a glycine load. The use of glycine-2-C^{14} with a glycine load, too, strikingly brings out these differences. (Relevant data with glycine-2-C^{14} in tracer doses are not available.)

The pattern of inhomogeneity thus demonstrated seems to be fairly consistent, at least in the limited number of cases so far studied. Whereas gouty subjects whose urinary uric acid output is within the limits of normal variation ("normal excretors") give a pattern of glycine incorporation into uric acid ordinarily indistinguishable from that of the normal,* the incorporation of glycine into uric acid in gouty "hyperexcretors" is abnormally great for some days after administration of isotope-labeled glycine.

It has not been made clear whether this inhomogeneity of patients with primary gout is attributable to quantitative or qualitative differences among them, i.e., whether the dissimilar patterns of glycine incorporation into uric acid reflect varying degrees of a common metabolic aberration or are the result of different errors of metabolism affecting alternative pathways. Analysis of our data implicates alternative pathways of glycine utilization for the biosynthesis of uric acid and directs attention to these pathways.

Role of "Shunt" Pathways of Purine Biosynthesis in Primary Gout, with Special Reference to "Hyperexcretors." The initial studies of "hyperexcretor" gouty subjects showing excessive incorporation of glycine-N^{15} into uric acid at a rapid rate implicated "shunt" pathways not

* Our results do not confirm the initial report of Wyngaarden [*10*] that gouty patients excreting normal amounts of uric acid in the urine consistently incorporate greater than normal amounts of glycine-1-C^{14} when given in tracer doses. In the two control subjects of Wyngaarden's study, 0.15 and 0.18 per cent of the dose, respectively, was excreted as uric acid in eight days, which is in agreement with the results observed in the four non-gouty control subjects of the present study. However, whereas the three "normal excretor" gouty patients of our report incorporated no greater amounts, all five "normal excretor" gouty subjects of Wyngaarden's study excreted at least 0.29 per cent of the dose in six or seven days. The patient who showed the highest incorporation in the latter group had some evidence of diminished renal function but renal damage was not present to a significant extent in any of the other cases.

Further, in spite of the similar cumulative excretions in the control subjects of Wyngaarden's study and the present one, peaking in the specific activity curves observed during the first few days in our non-gouty subjects was not in evidence in Wyngaarden's two control cases.

It would appear that the pattern and magnitude of glycine-1-C^{14} incorporation into uric acid exhibit wider variations than can be defined on the basis of the mere handful of cases studied thus far. Nevertheless it seems clear from our results, the similar findings of Seegmiller et al. [*11*], and the subsequent report of Wyngaarden [*12*] that at least some "normal excretor" gouty patients do not incorporate increased amounts of glycine-1-C^{14} into uric acid.

involving nucleic acid synthesis and degradation [*6,7*]. This interpretation is supported by the similar findings in the present studies of gouty "hyperexcretors," irrespective of whether they were given glycine-N^{15}, glycine-1-C^{14} in tracer or load doses, or glycine-2-C^{14} in load doses. Moreover, the uric acid-C^{14} and -N^{15} specific activities in such subjects fell to normal or lower than normal levels within a week or two at most, again indicating that the increased incorporation of glycine predominantly involved uric acid precursors with a short metabolic life span. "Shunt" pathways are operative also in "normal excretor" gouty patients (and in non-gouty subjects). This is particularly evident after administration of tracer doses of carbon-labeled glycine, since maximum specific activities occur within the first few days. In contrast to "hyperexcretor" gouty patients, however, the curves of glycine incorporation into uric acid in "normal excretor" gouty subjects do not disclose excessive activity of "shunt" pathways. Moreover, in both "normal excretor" gouty patients and non-gouty subjects the operation of "shunt" pathways, as indicated by glycine incorporation curves with tracer doses of carbon-labeled glycine, is more readily "saturated" and masked by loading doses of glycine.

It must be emphasized that in patients with primary gout, as in normal man, only a part of the glycine contributing to uric acid biosynthesis is incorporated directly by "shunt" pathways since the urinary excretion of isotope-labeled uric acid persists at an appreciable rate for many weeks. Nevertheless, the chief metabolic anomaly in patients with primary gout, at least in "hyperexcretors," appears to involve "shunt" pathways for the utilization of glycine carbon and nitrogen in the biosynthesis of uric acid. These pathways of biosynthesis will now be considered in this connection.

Pathways Effecting Direct Incorporation of Intact Glycine into Uric Acid C-4, C-5 and N-7. Inquiry into the nature of the metabolic aberration in primary gout has thus far been concerned largely with pathways effecting direct incorporation of intact glycine into the purine ring. As Buchanan [*6*] and Greenberg [*7*] have demonstrated in the pigeon and rat, intact glycine serves as a nucleus for the stepwise de novo synthesis of inosinic acid, contributing carbon-1 to carbon-4 of the purine ring, glycine carbon-2 to purine carbon-5, and the amino nitrogen of glycine to purine N-7. Seegmiller, Laster and Stetten [*17*] have provided evidence that this pathway also operates in man. After feeding 4-amino-5-imidazolecarboxamide-4-C^{13} the urinary uric acid was found to be quickly and richly labeled; this substantiates the proximate position of 4-amino-5-imidazolecarboxamide ribotide (which is formed from glycine) in the elaboration of uric acid from glycine in man.*

Pathways for the Incorporation of Nitrogen Derived from Glycine into Positions Other Than Uric Acid N-7. Not only does glycine provide C-4, C-5 and N-7 of the purine ring by *direct* incorporation of intact precursor but it contributes also to all the other nitrogen and carbon positions, by *indirect* pathways involving prior changes in the glycine molecule. In their initial study of a normal human subject Shemin and Rittenberg [*2*] noted that a substantial proportion of the total glycine-N incorporated into uric acid was present in positions 1 + 3 + 9: about 23 per cent on the first day, 25 per cent on the fourth day, 35 per cent on the ninth day, and 41 per cent on the fourteenth day. The pathways involved in the incorporation of nitrogen into positions 1, 3 and 9 in the de novo synthesis of purines have since been elucidated [*3*]. Stated in the sequence of incorporation, N-9 of the purine ring derives from the amide nitrogen of glutamine and is introduced in the reaction of 5-phosphoribosylamine with glycine to form glycinamide ribotide. N-3 of the purine ring also derives from glutamine, in the formation of formyl-glycinamidine ribotide from formyl-glycinamide ribotide. Aspartic acid is the donor of N-1 to form 5-amino-4-imidazole(N-succinyl-carboxamide) ribotide from 5-aminoimidazole ribotide. (That glycine may contribute nitrogen to glutamine and aspartic acid has long been apparent.) The purine ring is completed by the addition of carbon in position 2, converting the aminoimidazole carboxamide ribotide to inosinic acid.

The incorporation of glycine nitrogen into positions 1, 3 and 9 in addition to position 7 of the uric acid molecule would be expected to result in N^{15}/C^{14} ratios > 1.0, when glycine-1-C^{14},N^{15} is administered, if the carboxyl carbon

* In three gouty subjects these investigators found abnormally high incorporation of 4-amino-5-imidazole-carboxamide-4-C^{13} into uric acid [*18*]. It was pointed out, however, that the difference in some instances was not great [*18*]. It is therefore not clear yet how much of the metabolic defect in primary gout can be assigned to steps leading from 4-amino-5-imidazolecarboxamide ribotide to uric acid.

TABLE IV

ESTIMATED $\frac{N^{15}\text{-}7}{\text{TOTAL } C^{14}}$ RATIOS IN TWO NON-GOUTY SUBJECTS

Day	Per cent $\frac{N^{15}\text{-}7}{\text{Total } N^{15}}$*	$\frac{N^{15}\text{-}7}{\text{Total } C^{14}}$†	
		Case L. C.	Case T. G.
1	77	1.20	1.16
2	..	1.92	1.27
3	..	1.44	1.37
4	75	1.23	0.86
5	..	1.22	1.28
6	..	1.08	1.05
7	..	1.30	1.13
9	65	....	....

* Ratios obtained in a normal subject by Shemin and Rittenberg [2].

† Ratios estimated from the observed $\frac{\text{total } N^{15}}{\text{total } C^{14}}$ ratios in non-gouty subjects L. C. and T. G., assuming the same $\frac{N^{15}\text{-}7}{\text{total } N^{15}}$ ratio as in the normal subject of Shemin and Rittenberg on the days indicated.

of glycine is assumed to localize solely in C-4 of the purine ring. However, the results of the present study cannot be accounted for simply on this basis since the uric acid degradation studies in A. R. revealed that the incorporation of glycine-N^{15} into uric acid N-7 alone exceeded the total C^{14} incorporation. In A. R. (a "normal excretor" gouty subject) the uric acid N^{15}-7/total C^{14} ratios were generally in excess of 1.2. These high ratios might have been due to an error in the dose of C^{14} or N^{15}. However, the N^{15}-7/C^{14} ratios in our two control subjects (L. C. and T. G.), although not determined, have been estimated from the observed uric acid N^{15}/C^{14} ratios and the N^{15}-7/total N^{15} distribution in the control subject of Shemin and Rittenberg* (Table IV), and were found to be in excess of 1.0. Moreover, the N^{15}/-1-C^{14} ratios of 2.4 and 2.8 in the "hyperexcretor" gouty subjects indicate that at least 71 and 74 per cent, respectively, of the uric acid N^{15} would have had to be localized in positions 1 + 3 + 9 to produce N^{15}-7/C^{14} ratios of 1.0. The distribution of N^{15} in the uric acid of these two latter subjects was not determined yet the data available do permit the inference that *either* the "hyperexcretor" gouty subject depends to a much greater extent on glycine nitrogen for uric acid N-1,3,9 than does the non-gouty subject *or* that uric acid may be synthesized in part by a pathway which does not involve incorporation of glycine C-1, C-2 and N as such into uric acid C-4, C-5 and N-7, respectively (in which event the N^{15}-7/C^{14} ratio could exceed unity). The data available at present do not permit a distinction between these two alternatives. Additional N^{15} and C^{14} distribution studies in degraded uric acid samples are being undertaken to provide further information concerning the specific localization of isotope.

* Similar distributions were found in the two normal subjects studied by Seegmiller et al. [17].

Pathways for the Incorporation of the Carbon Atoms of Glycine Other Than by Direct Incorporation of Intact Glycine. There is evidence to suggest that there are alternative pathways for the utilization of glycine for uric acid biosynthesis, pathways which operate in addition to those effecting *direct* incorporation of C-1, C-2 and N of intact glycine into uric acid C-4, C-5 and N-7. Karlssen and Barker [19] found that 31.8 per cent of the C^{14} administered to pigeons as glycine-2-C^{14} was recovered in C-5 and 9.3 per cent was recovered in C-4 of the excreted uric acid. A clue to one pathway involved is provided by the studies of Nemeth, Russell and Shemin [5] in pigeons in which significant labeling of uric acid C-4 was observed seventy-two hours after the feeding of δ-aminolevulinic acid-5-C^{14}, the C-5 of which is derived from the α-carbon of glycine.

The recovery of the glycine α-carbon in C-4 of uric acid obviously excludes incorporation of the glycine carboxyl carbon in the same position, indicating that at least some fraction of uric acid precursors must be utilized for biosynthesis by a pathway which does not involve incorporation of the intact glycine molecule into uric acid positions 4, 5 and 7.

The greater isotope enrichment of uric acid after administration of glycine-2-C^{14} than after an equivalent dose of glycine-1-C^{14} might have been anticipated, without reference to incorporation in C-4, on the basis of the known contributions of the α-carbon of glycine to positions 2, 8 and 6 [20,21]. The conspicuously high specific activities in the uric acid of gouty "hyperexcretors" fed load doses of glycine-2-C^{14}, as opposed to glycine-1-C^{14}, again direct attention to the possibility that the metabolic

abnormalities in gout are concerned at least in part with "alternative" pathways of uric acid biosynthesis (those not involving direct incorporation of intact glycine). However, as already indicated, the high uric acid N^{15}/C^{14} ratios observed can be equally well explained if gouty "hyperexcretors" utilize significantly more than normal glycine nitrogen for uric acid positions 1, 3 and 9. Definite conclusions on this point must await further studies of isotope distribution in degraded uric acid samples.

APPENDIX

On the basis of certain assumptions, the data presented here permit an estimate of the size of the glycine pool. If it is assumed that the rate of distribution of the labeled glycine molecules throughout the miscible glycine pool is rapid compared to the rate of turnover of the pool, then the quantity of labeled uric acid precursors formed per unit time, K, is given by

$$K = \alpha G_{pool} \quad (1)$$

where α is the fraction of the endogenous glycine pool, (G_{pool}), being utilized for synthesis of uric acid precursors per unit time. Now if the glycine pool is increased by administration of a dose of glycine, G_{dose}, and it is assumed further that moderate increases in pool size do not result in a significant change in the amount of glycine utilized for synthesis of uric acid precursors, then

$$K = \beta(G_{pool} + G_{dose}) \quad (2)$$

where β is the fraction of the augmented glycine pool utilized for synthesis of uric acid precursors per unit time.

From (1) and (2)

$$G_{pool} = \frac{\beta}{\alpha - \beta} G_{dose}$$

Now the ratio $\frac{\alpha}{\beta}$ should be proportional to the ratio of isotope incorporation under tracer and load conditions respectively. In control subjects the ratio, -1-C^{14} tracer/-1-C^{14} load, in uric acid averaged 2.2 for the first three days. Since G_{dose} was 100 mg./kg. for all but one subject, an average value of 83 mg./kg. for G_{pool} results. This must represent a maximal estimate since K might be expected to increase with increase in the glycine pool. Since the excretion of uric acid was not increased significantly following administration of the loading doses of glycine, evidence for an increase in K is lacking but inasmuch as the "shunt" pathway accounts only for part of the glycine incorporation into uric acid, the absence of an immediate increase in uric acid excretion is of questionable significance. It has been shown that a high protein diet increases both the uric acid excretion and the magnitude of glycine-N^{15} incorporation into uric acid [*22*]. Furthermore, different pathways of biosynthesis may predominate under different experimental conditions. Thus these calculations can yield at best only a rough approximation of the size of the glycine pool. Nevertheless, the value obtained is in good agreement with that of 90 mg./kg. reported recently by Crawhall and Watts [*23*], as calculated from measurements of the specific activity of free glycine in the urine following glycine-N^{15} administration.

SUMMARY AND CONCLUSIONS

1. Isotope incorporation into the urinary uric acid following administration of glycine-1-C^{14} or glycine-2-C^{14} with or without glycine-N^{15} was studied in twenty-three subjects. Of these, thirteen were non-gouty (including two with azotemia), five had primary gout *without* excessive urinary uric acid excretion ("normal excretors"), five had primary gout *with* excessive urinary uric acid excretion ("hyperexcretors").

2. In confirmation of previous studies with glycine-N^{15}, the initial incorporation of glycine labeled with C^{14} or N^{15} into uric acid was significantly greater in gouty "hyperexcretors" than in normal subjects; whereas the pattern of incorporation in gouty "normal excretors" was indistinguishable from the normal. In non-gouty azotemic subjects the specific activity of the uric acid after administration of glycine-1-C^{14} was found to be somewhat greater than normal.

3. The administration of a glycine load, 100 or 150 mg./kg. body weight, together with glycine-1-C^{14} or glycine-2-C^{14} significantly reduced the incorporation of C^{14} into uric acid in all groups of subjects. "Saturation" of "shunt" pathways by these glycine loads was more complete in normal subjects and "normal excretor" gouty patients than in gouty "hyperexcretors." From the ratio of isotope incorporation under tracer and load conditions the glycine pool could be estimated; this was found to approximate a mean value of 83 mg./kg. body weight.

4. Glycine-2-C^{14} incorporation into uric acid was significantly greater than glycine-1-C^{14} incorporation at tracer and load levels in all groups of subjects; this finding is in accord with the known contribution of the α-carbon of glycine to every carbon of the uric acid molecule. The disproportionate enrichment of isotope after administration of glycine-2-C^{14} (with a glycine load) was particularly marked in gouty "hyperexcretors."

5. In double-label experiments, glycine-N^{15} incorporation into uric acid was considerably in

excess of glycine-1-C^{14} incorporation in all groups of subjects. The initial N^{15}/-1-C^{14} ratios averaged about 1.7 and 1.8 in two non-gouty subjects, 2.0 in one gouty "normal excretor," and 2.4 and 2.8, respectively, in two gouty "hyperexcretors." From the determined N^{15}-7/total N^{15} and N^{15}-7/total C^{14} ratios in one case, and estimated ratios in others, it could be deduced that glycine-N^{15} localizes in uric acid N-7 in part by pathways other than those immediately concerned with the direct incorporation of carbon-1, carbon-2 and the nitrogen of intact glycine into positions 4, 5, and 7, respectively, of the purine ring. Evidence from the literature is cited in support of the operation of such pathways.

6. Two alternative interpretations of the findings in gouty "hyperexcretors" are offered: (1) that a disproportionately large fraction of glycine nitrogen is utilized for positions 1, 3 and 9 of the purine ring; and (2) that glycine contributes its nitrogen to position 7 of the purine ring not only by direct incorporation of the glycine molecule in toto but also by other as yet undetermined pathways.

Acknowledgment: We are greatly indebted to Dr. Lena Sharney and Mr. James J. Hay of the Department of Physics, The Mount Sinai Hospital, for assistance in the operation of the mass spectrometer for estimation of uric acid atom per cent excess N^{15}, and to Dr. Bernard Weissmann for degradation of uric acid samples.

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Review

Dominance and Recessivity in Medical Genetics*

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WHEN a physician or surgeon is confronted with an inherited abnormality, he usually makes an attempt to classify it as dominant or recessive, according to which of the typical family trees shown in textbooks its appearance corresponds. If, as quite often happens, the observations do not fit either of these categories, he concludes that the gene has "incomplete penetrance." This is an oversimplification of the problem. It can be shown that many, if not all, of the abnormal human characters which have been described as dominants are not, in fact, dominant in the original and correct sense in which that word was used. Furthermore, in man, as in other species, dominance is not fixed, but is dependent upon the conditions under which genes exert their effects. In fact, human material provides some of the most interesting examples of dominance modification in all genetics.

One of the first points brought out by Mendel's experiments was that two contrasting characters, when brought together in a cross, differ markedly in their ability to express themselves in the resulting hybrid offspring. When he crossed a pure-breeding red-flowered pea, for instance, with a pure-breeding white-flowered one, the progeny were found to resemble the red-flowered plant. Mendel knew that whiteness had not been eliminated, for in the subsequent generation white-flowered plants appeared again; but in the hybrid, whiteness seemed to recede from view and redness to dominate. Mendel therefore called a trait such as redness in pea flowers dominant, and a trait such as whiteness in pea flowers, recessive.

We can therefore define dominance as the situation in which the heterozygote (hybrid) is indistinguishable from one of the homozygous (pure-breeding) parents. This definition has been accepted in most textbooks of human genetics. Thus, Stern [*1*] defines dominance as the type of inheritance in which "the heterozygote exhibits the properties typical for one of the two alleles only," and Neel and Schull [*2a*] state that "it is customary to refer to a gene, *A*, as being dominant to an allele, *a*, when it is impossible by any known test to distinguish between *AA* and *Aa* individuals. . . . Most of the published reports concerned with heredity in man involve simple dominant inheritance." However, Levit [*2b*] and Ford [*3*] has pointed out that in man the statement that an abnormality shows dominant inheritance is nearly always an assumption. This is so because persons carrying a double dose of the abnormal gene will appear only extremely rarely, so that there will, as a rule, be no opportunity for comparing the effects of the gene in a single and double dose.

Without such direct evidence, it cannot be assumed that characters are truly dominant. Early in the study of experimental genetics it became apparent that dominance of the classical mendelian type was far from universal. A red snapdragon, for instance, crossed with a white-flowered one gives first generation hybrids all of which have pink flowers. In the same way, a black Andalusion fowl bred with a splashed white one produces offspring with "blue" plumage. In other instances, the hybrid offspring may resemble one parent more closely than the other. Hence, there may be all stages between complete dominance and the absence of dominance, and these various conditions may all be found among the different traits of a single individual.

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The term "dominant" has thus come to be employed loosely, some authors using it in the sense given, to mean that the heterozygote is indistinguishable from one homozygote, while others have called dominant any gene whose effects in the heterozygote can be distinguished at all. The so-called dominant mutations in the fruit-fly, Drosophila, are either lethal in double dose, or their heterozygous expression is less extreme than their homozygous. Evidence will be adduced herein that this is true also of the so-called dominant abnormalities in man, in spite of the general acceptance of the classic mendelian definition of dominance by human geneticists.

The second point to be borne in mind is that it is not the gene itself, but the *character* controlled by the gene, which may be dominant, recessive or intermediate. This may seem a pedantic distinction, but it is important for two reasons. First, a gene may have pleiotropic effects; in other words, it may control several characters, some of which are dominant or intermediate and others recessive. This statement remains true in spite of the finding that many pleiotropisms are "spurious," i.e., are due to a single biochemical change. This change will have different effects in different tissues and organs, the effects depending upon the physiological state of the tissues or organs involved, which is itself under genetic control. Thus, Dobzhansky [*4*] showed that the genes of the white-eye series in Drosophila affect the shape of the spermatheca. The genes are all recessive to wild type as regards their effects on the eye, but show intermediate expression as regards the effect on the spermatheca. A similar situation is found in fibrocystic disease of the pancreas in man: the abnormal gene produces an observable effect on the pancreas only when present in double dose, but when present in a single dose may lead to increased loss of sodium and chloride in the sweat [*5*].

Dominance is not a fixed property of a gene, but is modifiable in several ways. Early in the study of experimental genetics it became clear that the effects of many genes are not constant but are modified, often to a great extent by the presence or absence of other genes. In 1928 Fisher [*6*] pointed out that if modifiers enhanced or suppressed the effects of a gene in single dose, the heterozygote would resemble one homozygote and the character would become dominant or recessive. The hypothesis was soon confirmed experimentally and only a few examples need be quoted. In fowls, Landauer [*7*] found that the gene for frizzled plumage, the single dose effects of which are normally intermediate, is converted into an almost complete recessive by the presence of a particular modifier in double dose. Dunn and Landauer [*8,9*], with the gene rumpless, which reduces the tail and posterior end of the body, were able to go further and show that this could be converted into either a dominant or a recessive by crossing to different stocks, followed by selection for dominance or recessivity. Ford [*10*] was able to modify the dominance of a character in the currant-moth, Abraxas grossulariata. There is a single wild variety (lutea) with yellow instead of white ground color, which normally gives an intermediate offspring when crossed with the wild type. By four generations of plus or minus selection, Ford was able to confer nearly complete dominance or recessivity upon the character, whichever was desired. Fisher and Holt [*11*] were also able to achieve by selection a rapid change in the dominance relationships of the short-tailed character in mice. Dominance modification is not uncommon in plants and examples are quoted by Harland and Atteck [*12*].

An alternative method of dominance modification was proposed by Haldane [*13,14*]. He pointed out that most genes probably act by producing enzymes, and that these will operate effectively only up to a saturation level, above which further enzyme production will have no detectable effect. Haldane pointed out that different genes at the same locus might vary in their quantitative effects on enzyme production. Selection would then favor those genes whose activity was sufficient to raise enzyme production to saturation level even in single dose. In other words, the metabolism of the heterozygote would then be as efficient as that of the homozygote and the character would be dominant. Dominance would thus arise through a substitution of the gene itself, through selection of one rather than another member of a series of genes at the same locus, and not through selection of modifiers at other loci. The application of Fisher's and Haldane's theories of dominance modification to some human characters is discussed later.

Differences in Single and Double Dose Expressions of Abnormal Human Genes. The most favorable series of examples for comparison of the effects of mutant human genes in single and double dose is the group of conditions associated with

abnormal hemoglobins. It had been known for years that some cases of thalassaemia are mild and others severe. Neel and Valentine [*15*] produced evidence that the mild cases are heterozygous, and the severe cases homozygous for the thalassaemia gene. In 1949 Neel [*16*] showed that a similar situation obtains in the case of a sickle cell gene. Persons who are heterozygous for the sickle cell gene have the sickle cell trait, which can be recognized by artificially deoxygenating samples of blood, when sickling of erythrocytes occurs, or by electrophoretic analysis, which shows the presence of sickle cell as well as normal adult hemoglobin. Carriers of the sickle cell trait are perfectly healthy under physiological conditions. They show, however, an inability to concentrate their urine in response to dehydration [*17*], and in environments in which the oxygen tensions are unusually low, as in high altitude flights in unpressurized aircraft, carriers of the sickle cell trait are liable to develop intravascular sickling with splenic infarction [*18*]. Persons who are heterozygous for the hemoglobin C gene are quite healthy, although they show "target cells" in the circulating blood and, on electrophoresis, some hemoglobin C, whereas those who are homozygous for the gene have a hemolytic disease [*19*]. Similarly, those who are heterozygous for the hemoglobin E gene are detectable only by electrophoretic studies, whereas the homozygotes show a fairly well defined syndrome with polycythemia, numerous target cells and sometimes anemia [*20,21*]. In all these cases, then, the effects of the abnormal genes in single dose are recognizable but are quite different from the severe effects produced by the genes in double dose. Thus the single dose expression is intermediate and there is no true dominance.

Since most abnormal genes are rare, in the great majority of cases they are seen only in the heterozygous phase. There will then be no opportunity to compare the effects in the abnormal homozygote with those in the heterozygote. However, occasional matings (usually consanguineous) will be found in which both partners carry the abnormality. In the absence of lethal effects, the expectation is that one quarter of the offspring of such matings will be homozygous for the abnormal gene, one-half will be—like the parents—heterozygous, and one-quarter will be normal. If, then, a minority of the offspring show effects of the abnormal gene which are much more severe than those in their siblings and parents, it is probable (but not certain) that the severe effects are due to the presence of the abnormal gene in double dose. Reports of a number of families exhibiting this mode of inheritance have been published. The first, which has often been quoted, is a family described by Mohr and Wriedt [*22*]. There was a consanguineous marriage between two people who had a relatively mild degree of brachyphalangy. One of the children died when one year of age, with absence of fingers and toes and "her whole osseous system in disorder." Other children showed a relatively mild defect, like the parents.

Snyder and Doan [*23*] described a family in which the inheritance of telangiectasia appeared to be controlled by autosomal gene with moderate single-dose expression. Two affected individuals married and produced a child with severe multiple telangiectases, both internal and external, who died from uncontrollable bleeding when aged two and a half months.

Böök [*24*] described a large family with chondrodystrophy. Most of the subjects showed the moderate heterozygous manifestation of the autosomal gene concerned (chondrohypoplasia). There was a first cousin marriage between affected persons. Two of the three children showed the disease in the mild form present in other affected members of the family. The third child was much more severely affected, with shortened and deformed limbs. The author plausibly concludes that this child may have had a double dose of the chondrodystrophic gene.

Haverkamp-Begemann and van Lookeren-Campagne [*25*] investigated a family showing the Pelger-Huët anomaly, in which the nuclei of neutrophil leukocytes are not segmented, but are staff- or spectacle-shaped. The inheritance is controlled by a single autosomal gene, with somewhat variable heterozygous manifestations [*26*]. In the family under consideration, both parents, who were first cousins, and two of five living children were found to have the typical Pelger-Huët anomaly. A third child, a girl aged two and a half years, showed a different picture. The neutrophil nuclei were round and the chromatin was coarse and fragmented; they resembled the nuclei of rabbits homozygous for the Pelger-Huët gene [*27*]. It was therefore concluded that the propositus might have the Pelger-Huët gene in double dose. However, she was otherwise normal, apart from a tendency to epileptiform attacks which was probably

incidental. In rabbits the Pelger-Huët gene is lethal in double dose, the few animals that survive after birth being small and showing skeletal deformities.

Johnson and Falls [*28*] describe the offspring of a marriage between cousins both of whom had a relatively mild form of epidermolysis bullosa. Two of eight children showed the abnormal syndrome in a very severe form and may have had double doses of the gene concerned.

Aschner, Curth and Gross [*29*] reviewed 234 cases of psoriasis, in which there was a high family incidence. The penetrance of the gene or genes responsible for psoriasis was found to vary from pedigree to pedigree; usually the mode of inheritance was of the "simple dominant" type. In one family both parents and two of five children were affected. One of the affected children had a relatively mild disease, like the parents, while a second had a severe generalized psoriasis starting in early childhood. This child may have been homozygous for a gene predisposing the subject to psoriasis, as may some other patients with severe generalized psoriasis quoted by the authors.

Welander [*30*] describes a family in which the inheritance of distal myopathy appeared to be controlled by a single autosomal gene with heterozygous effects. Both parents had symptoms of the disease, wasting of the long extensors and the small muscles of the distal parts of the limbs. Three of sixteen children were affected in a grossly atypical manner, with early and severe involvement of the distal long flexors and proximal limb muscles. This may be a homozygous manifestation of the distal myopathy gene.

Allison and Blumberg [*31*] describe two families in which the appearance of an osteoarthropathy of the phalanges of the hands was controlled by an autosomal gene with a high rate of penetrance in the heterozygous phase. Two of six offspring of a first cousin marriage between affected persons had a much more severe deformity than the rest.

Modification of Single-Dose Expression of Human Genes. In the case of the genes for abnormal hemoglobins it is certain that the single- and double-dose expressions are different, and in the other examples quoted this is also the simplest explanation of the reported observations. An alternative explanation is that the single-dose expression of the abnormal gene is highly variable, this variability itself being in part under genetic control. On this hypothesis, the single-dose effects are reduced or "buffered" by other common genes in the population. Occasionally, and especially in some of the offspring of consanguineous matings, the "buffering" genes would be absent, and then the single-dose effects of the abnormal gene would be much more severe than usual. It is unlikely that a mechanism of this kind could have been responsible for all the examples quoted, but it might explain some other findings. Thus, Böök and Fraccaro [*32*] described a consanguineous mating in a North Swedish family with mandibulofacial dysostosis. The mother and three of six children were affected. Two of the affected children had much more severe involvement than other members of the family and died at the ages of one and two months, respectively. The father was apparently normal. As the authors conclude, the simplest and most likely explanation is that a gene with variable heterozygous expression is responsible for all the abnormalities; the extreme involvement and death of two children could be due to the loss of a modifier which reduces the severity of the single-dose expression. It is also possible, but less likely, that the father carried the abnormal gene in double dose.

Considerable variability in the single-dose expression in the female of the gene for sex-linked ocular albinism is known. Waardenburg and Van den Bosch [*33*] described a large family in which affected males showed marked reduction in the pigment of the tapetum combined with hypoplasia of the fovea and secondary nystagmus. The female carriers were recognizable by diascleral translucency of their irides and by irregular peripheral pigmentation of the fundi, a point which will be discussed later. However, one female who was undoubtedly heterozygous for the gene was as severely affected as the homozygous males.

One of the most striking examples in all genetics of a single gene modifying the heterozygous expression of another gene is again provided by observations on the abnormal human hemoglobins. In persons heterozygous for the sickle cell gene, about 20 to 45 per cent of the hemoglobin formed is of the sickle cell type, the remainder being of the normal adult type [*34,35*]. (Fig. 1, upper left.) The proportion of abnormal hemoglobin appears to be controlled by modifiers which are autosomal and independent of the sickle cell gene. In the sickle cell homozygote, the great majority of hemoglobin is of the sickle

cell type, the remainder being of the fetal type. (Fig. 1, upper right.) However, in persons heterozygous for both the sickle cell and thalassemia genes (which are at different loci), very little (Fig. 1, lower left) or no normal adult hemoglobin (Fig. 1, lower right) is formed, as shown by Sturgeon, Itano and Valentine [*36*] and others. The sickle cell heterozygote in the presence of the thalassemia gene is thus often biochemically and clinically indistinguishable from the sickle cell homozygote, in other words, the sickle cell character behaves as a dominant. The thalassemia gene also magnifies the expression of the hemoglobin C gene in the heterozygous phase [*37*]. The relationship of the thalassemia gene to the appearance of hemoglogin H is also relevant. The genetics are not yet fully worked out and two hypotheses fit the observations, which are that one parent and some siblings of persons with hemoglobin H are hematologically normal while the other parent and siblings have a blood picture like the thalassemia trait [*38*]. Possible explanations for this situation are: (1) that persons carrying a single dose of the hemoglobin H gene are normal, in other words the character is completely recessive, except in the presence of any thalassemia gene, when the recessivity is broken down and hemoglobin H is formed; (2) that one particular type of thalassemia gene carries with it the potentiality to produce hemoglobin H, but that this potentiality is only realized in the presence of one or more modifiers. On either hypothesis interaction between different genes breaks down the recessivity of the hemoglobin H character, in other words a modification of dominance relationships takes place. Similarly, Gunther and Penrose [*39*] found that the great variation observed in the single-dose expression of the gene for epiloia was at least partly due to independent modifying factors.

The examples which have been quoted illustrate how the single-dose expression of abnormal human genes can be increased by the presence of modifiers at other loci. The opposite effect, diminution of single-dose expression of abnormal genes by modifiers, converting the character into a complete or nearly complete recessive, is much more common. It is responsible for the "incomplete penetrance" often observed, when a "dominant" character seems to skip one or two generations and then reappear. This has been described, for instance, in the dystrophic form of epidermolysis bullosa [*40*] in diabetes insipidus

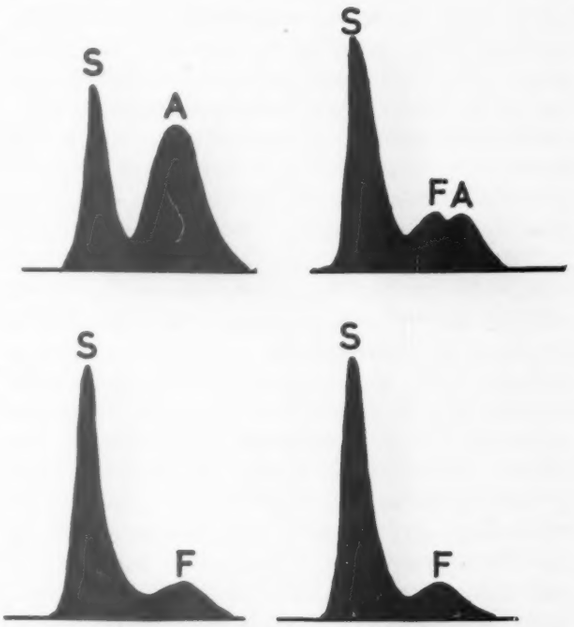


FIG. 1. Electrophoretic patterns of hemoglobin. In upper left, sickle-cell heterozygote; upper right, sickle-cell homozygote; and lower left and right, persons heterozygous for both the sickle cell and thalassaemia genes. The types of hemoglobin are as follows: A = normal adult, F = fetal and S = sickle cell.

[*41*] and in hereditary methemoglobinemia [*42*]. An interesting example of variable penetrance is that of myopia, the inheritance of which is controlled by a sex-linked gene. There is considerable variation in penetrance from family to family, and in a single family the character has been described as behaving as a "dominant" in the one branch and as a "recessive" in the other [*43*].

These situations are often dismissed as exceptions to the regular type of inheritance exhibited by "good" characters. Nevertheless, they provide partially controlled experiments of considerable interest, for here we have the same gene introduced into different gene complexes with profound effects on its expression. The discovery of similar phenomena in the blood groups has attracted wider interest and has allowed a more precise analysis of the genetic mechanism involved. The studies of Schiff and Sasaki [*44*] showed that the A and B blood group antigens appear in the saliva and other body fluids only when the secretor gene is present; this gene has no influence on the ABH antigens of red cells. Levine et al. [*45*] have identified a rare gene, *x*, which, when present in double dose, suppresses the B and O antigens in the

saliva and red cells of persons carrying the corresponding blood group genes. Weiner and co-workers [*46*] have described another rare gene, *y*, which, when present in double dose, inhibits the development of the A antigen in the red cells and, to a lesser extent, in the saliva of persons heterozygous for the *A* gene. These are interesting examples of dominance modification.

Sex Controlled Dominance. A well known instance of the fact that genes produce different effects in different internal environments is provided by sex-controlled inheritance. This is the condition in which the action of an autosomal gene is detectable only (or more frequently) in the environment provided by one of the sexes. It has to be distinguished from sex-linked inheritance, in which the genes themselves are carried in the sex chromosomes. Many totally sex-controlled genes are known in lower animals. Thus, the difference between horned and hornless sheep depends upon the presence or absence of a single autosomal gene, but whereas a single dose of the gene will produce horns in rams, a double-dose is necessary in ewes [*47*]. In man, genes for white forelock and premature baldness have been described which in single dose produce an effect in males only but in double dose affect females [*48*]. Hersh and his colleagues [*49*] report that ankylosing spondylitis has a 70 per cent penetrance in males and 10 per cent in females. Hemochromatosis is also much more common in males, presumably because females lose iron through menstruation. Conversely, Stecher [*50*] reports that the inheritance of Heberden's nodes is usually of the "dominant" type in women, but is recessive in men.

Haldane's Theory of the Evolution of Dominance. The examples which have been quoted show how the dominance of human characters can be altered by genes at other loci. Haldane's suggestion that dominance could arise through a change in the gene itself, through selection of one rather than another member of a multiple allelomorph series, and not through selection of modifiers, is probably true of many normal human genes. Indeed, it must be a common method by which abnormal mutants are forced into recessivity. Thus, the normal allelomorph of the hemophilia gene, when present in single dose in female carriers, produces enough antihemophilic factor for efficient blood coagulation. Similarly, many metabolic defects in which single enzymes are wanting are inherited as recessives [*51*]; the normal gene in single dose produces enough enzyme for functional efficiency, although suitable tests may reveal the heterozygous carrier state. Thus, Hsia and Driscoll [*52*] have examined the apparently normal parents of children with phenylketonuria, which is produced by an autosomal gene in double dose. These heterozygous carriers of the phenylketonuria gene were found to have significantly higher blood levels of phenylalanine than normal subjects, although there was some overlap between the groups. The carriers are also unable to metabolize ingested phenylalanine as readily as normal subjects [*53*].

Again, sex-linked nephrogenic diabetes insipidus is a disease characterized by polyuria which dates from infancy and is resistant to vasopressin, renal function being otherwise normal. In patients not kept fully hydrated mental defects develop and they may die young. Carter and Simpkiss [*54*] found that the capacity to concentrate urine is significantly lower in female carriers of this gene than in normal subjects. The recognition of female carriers of the ocular albinism trait has already been discussed; and the mild, but distinctive, manifestations of xeroderma pigmentosum in a single dose are well known. The recognition of carriers of abnormal genes has obvious medical application, and has been achieved in many characters, as discussed by Neel [*55*] and Franchesetti and Klein [*56*].

Occasionally, the effects of the gene in single dose will be more severe. The appearance of the complete ocular albinism syndrome in female carriers has already been mentioned. Milch and Milch [*57*] point out that alcaptonuria, which is usually inherited as a recessive character due to the absence of the enzyme catalyzing homogentisic acid oxidation, sometimes appears in individuals who are heterozygous for the gene, so that the inheritance appears to correspond to the "dominant" pattern rather than the recessive. An alternative hypothesis, that different genes produce alcaptonuria, cannot explain all the observations, since in single families the character behaves sometimes like a "dominant," at other times like a "recessive."

In these instances the Haldane mechanism of dominance modification has clearly broken down: the normal gene in single dose has not reproduced the healthy metabolic pattern. But, as Ford [*58*] has pointed out, the saturation level for a given enzyme will be determined in relation to the residual gene complex, so that even here the action postulated by Fisher may be operative, although in some cases in addition to the

Haldane mechanism. In any case, both suggestions involve selection acting upo: other genes than the mutant.

It is very unlikely that abnormal genes could achieve dominance by Haldane's method. For selection would operate even more strongly against mutants producing large amounts of an abnormal product than those producing smaller amounts.

Modification of Dominance in Lower Animal and Human Populations. The examples which have been quoted illustrate how the dominance or recessivity of abnormal human characters depends upon genes at other loci. It is worth considering how far Fisher's general argument concerning dominance modification is applicable to human populations. Fisher reasoned as follows: mutation is always producing new genes, the majority of which will inevitably be deleterious, since in a delicately adjusted system like the gene-complex most changes are likely to be for the worse. Thus, the mutant genes will remain relatively rare in the population. Nevertheless, we know as an empirical fact that the majority of mutations are repeatedly produced, so that the organism will have a wide experience of them. It follows that, unless the mutant genes are so lethal that their bearers have no descendants, animals or plants will have an opportunity of modifying their response to them by adjustments of the gene-complex. Thus, the single-dose expression of the gene will be reduced, and the character will be forced into recessivity. The opposite tendency will occur in the case of advantageous mutations: the expression in the heterozygote will be so magnified that the character becomes dominant as the gene spreads through the population. Fisher's theory is borne out by studies of wild populations, which carry surprisingly large numbers of recessives on all but the sex chromosomes, where they would not be expected (e.g., Gordon [*59*] for Drosophila, and Sexton and Clark [*60*] for the small crustacean, Gammarus).

In general, artificial selection in domestic animals also tends to encourage complete dominance or recessivity, but the resulting dominance relationships are often quite different from those found in wild populations, tending to produce aberrant forms which are dominant to the "wild type." Thus, a viable dominant black form occurs in the guinea pig, and the hornless condition in cattle is nearly dominant; while in poultry the majority of "domestic" characters are dominant [*61*].

Selection for dominance or recessivity in man must have differed in important respects from that in either wild or domesticated animals. The perpetuation of moderately disadvantageous genes in man will tend to be increased by the fact that elimination of human carriers of abnormal traits will be less rigorous than elimination of comparably affected animals. This process is, however, to some extent offset by the fact that for social reasons some trait carriers will remain childless. In all human societies individuals must have been valued for qualities other than physical vigour. Thus from an early period in the evolution of mankind persons who would have been eliminated from the population as breeding units in the prehuman stage must have made a considerable contribution to posterity. Such a negation, or in some instances reversal, of selection will not only fail to produce the normal selective modification leading to dominance, but may break down dominance relationships previously attained, as Ford [*3*] has pointed out.

We should, therefore, expect to find in human populations numerous genes that mitigate the single-dose expression of other mutant genes, but that the process of forcing the mutants into recessivity would be much less complete than in wild populations of animals. As already pointed out, this seems to be the case. The majority of abnormal human characters are the heterozygous effects of mutant genes, the severity of the effects often being modifiable by genes at other loci. No example of true dominance, in which the single- and double-dose expressions of the abnormal gene are equivalent, is known. Furthermore, a high proportion of autosomal and sex-linked recessive characters in man show some single-dose expression. This must partly be due to the fact that small gene effects are more easy to detect in man (whose physiology and biochemistry are comparatively well known) than in other animals. But even well defined characters which are recessive in lower animals have intermediate expression in man. Thus, hereditary spherocytosis is present in man heterozygous for the gene, whereas in mice, only those homozygous for the gene show any abnormality of the red blood cells [*62*]. Thus man is unique in the animal kingdom in the low degree of success which selection for dominance or recessivity has attained.

It can be concluded in general that if an inherited character is abnormal (i.e., a rare disease) it is very unlikely to be a true dominant. There is a greater chance that dominance will

have evolved in common characters, when the spread of the genes concerned must have been facilitated by natural selection. But even in these situations dominance is exceptional in man. The *A* and *B* blood group genes are dominant to *O* in the sense that blood-group tests fail to distinguish between *AA* and *AO* or *BB* and *BO* subjects. But most other heterozygotes for blood-group alleles, e.g., *AB*, *MN*, *Kk* and Lu^a/Lu^b, can be distinguished from homozygotes. And, as already stated, the genes for abnormal hemoglobins produce distinct single- and double-dose effects, despite the fact that the characters are common or polymorphic in some populations.

The fact that true dominance is extremely rare in man raises the problem of terminology. The term "dominant inheritance" for characters which are intermediate and manifested in heterozygotes is so deeply ingrained that it will undoubtedly continue to be generally used. But then the definition given in lectures and textbooks will have to be altered in such a way as to make it clear that we are not dealing with dominance in the original mendelian sense. And this conclusion has a bearing on the development of a flexible notation for human genes, a problem briefly discussed by Allison [*63*].

SUMMARY

1. Whenever it has been possible to study the effects of abnormal human genes in double-dose, they have been found to be much more severe than the effects in single-dose. Hence these abnormal human genes are not dominant in the original sense of the word, by which it was meant that the effects of a gene in single- and double-dose were indistinguishable.

2. The single-dose expression of some human genes is known to be profoundly modified by genes at other loci. Thus, Fisher's theory of dominance modification is applicable to man. It is likely that the nearly complete dominance of many *normal* human characters arises through the mechanism postulated by Haldane, selection of genes which provide an adequate margin of safety in the production of enzymes. Nevertheless, even in situations in which dominance has arisen in this way, the dominance relationships may be altered by genes at other loci.

3. In human populations selection for dominance or recessivity seems to have been much less effective than in lower animals in the wild or under domestication. This is apparently due to the different way in which selection would exert its effects in human and lower animal populations.

Acknowledgment: We are indebted to Dr. E. B. Ford and Dr. A. G. Motulsky for reading the typescript and contributing some useful suggestions.

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Seminar on the Brain

Present Status of the Schizophrenia Problem

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THE Second International Congress for Psychiatry held in Zurich in 1957 bore the title, "The Present Status of Our Knowledge about the Group of Schizophrenias." This term was chosen because Bleuler had used it in 1911 in the title of his classic work on dementia praecox to emphasize an important aspect of his findings. That is, that the symptoms of schizophrenia arise from a number of unknown causes and that there are probably many different kinds of disorders included under the term schizophrenia.

The present paper will be devoted to the following problems: (1) diagnosis, particularly concerned with the selection of one or more groups with common symptoms that have a predictable course and outcome; (2) the role of heredity in schizophrenia; (3) the results of the search for psychologic, physiologic and biochemical abnormalities that may aid in differentiating one group of schizophrenic subjects from another and from non-schizophrenic control subjects; and (4) the status of the various empirical therapies for schizophrenia.

Bleuler's [*1*] definition is particularly relevant to the problems to be considered in this paper. "By the term 'dementia praecox' or 'schizophrenia' we designate a group of psychoses whose course is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full *restitutio ad integrum*. The disease is characterized by a specific type of alteration of thinking, feeling, and relation to the external world which appears nowhere else in this particular fashion.

"In every case we are confronted with a more or less clearcut splitting of the psychic functions. If the disease is marked, the personality loses its unity; at different times different psychic complexes seem to represent the personality. Integration of different psychic complexes and strivings appears insufficient or even lacking. The psychic complexes do not combine in a conglomeration of strivings with a unified resultant as they do in a healthy person; rather, one set of complexes dominates the personality for a time, while other groups of ideas or drives are 'split off' and seem either partly or completely impotent. Often ideas are only partially worked out, and fragments of ideas are connected in an illogical way to constitute a new idea. Concepts lose their completeness, seem to dispense with one or more of their essential components; indeed, in many cases they are only represented by a few truncated notions.

"Thus, the process of association often works with mere fragments of ideas and concepts. This results in associations which normal individuals will regard as incorrect, bizarre, and utterly unpredictable. Often thinking stops in the middle of a thought; or in the attempt to pass to another idea, it may suddenly cease altogether, at least as far as it is a conscious process (blocking). Instead of continuing the thought, new ideas crop up which neither the patient nor the observer can bring into any connection with the previous stream of thought."

Furthermore, Bleuler pointed out that the symptoms often appeared insidiously and progressed slowly with exacerbations and remissions. Consequently, diagnosis and prognosis were possible in many cases only after months and years of observation.

Psychatrists have reacted to this complex situation by taking extreme positions, largely dependent on whether their experience had been with cases of chronic schizophrenia in public hospitals or with early acute cases in private practice and in private hospitals.

Although many psychiatrists contend that the condition is still too poorly defined to make possible fruitful research in these complex disorders, a number of long term studies have been published in recent years that make it possible to resolve some of these controversies and to get on to orderly research.

Manfred Bleuler [*2*], who has continued his father's comprehensive studies of schizophrenia at Bergholzi, reported in 1941 on what had happened to 500 patients fifteen years after the first attack. One-fourth of the patients ended in dementia, one-fourth in marked personality deterioration, one-fourth in mild defect, and the remainder recovered usually in a few months and remained well. According to most authorities this constitutes the common outcome for any large undifferentiated series of schizophrenic patients.

DIFFERENTIATION OF SCHIZOPHRENIA FROM SCHIZOPHRENIFORM PSYCHOSIS

Many European psychiatrists [*3*], by carefully selecting cases according to the basic symptoms described by Bleuler, have been able to choose a group of cases that run a chronic course and have an unfavorable prognosis, and probably constitute a disease entity. Langfeldt [*4*] of Oslo has been a leader in this work. He reported at the Congress that cases chosen by these criteria in 1937 followed the predicted course and outcome in more than 90 per cent of subjects. Psychiatrists from Holland and Germany reported similar successes in selecting cases that followed a similar downhill course, "the true dementia praecox" or "process schizophrenia."

The American psychiatrists, particularly, reported on their inability to define such a group. Menninger [*5*] made a plea for abandoning the attempts to discover disease entities. He offered a new terminology for describing psychotic patients and suggested that the term schizophrenia be abandoned. He suggested that the concepts of nutriment derived from Piaget and of organ modes from Erikson supply the theoretical framework. Finally, he proposed a new classification of patients into four groups according to degrees of passivity and activity.

This difference of opinion about nosology was unresolved at the Congress but Langfeldt's data seemed to justify further attempts to differentiate the schizophrenias into schizophrenia and schizophreniform psychosis. Langfeldt stated that an independent follow-up of his cases was being made by two psychiatrists. This study by Eitinger, Laane and Langfeldt has been published [*6*]. Langfeldt's concepts are as follows:

The differential diagnosis depends on the psychological splitting phenomena taking place in patients while they retain clear consciousness. To the splitting phenomena belong clear ideas and feelings of passivity, of outside control, derealization and depersonalization. The patient often accepts these experiences without comment.

Patients with the schizophreniform psychosis, in contrast, often have clouding of consciousness, much emotional display and usually acute onset, frequently associated with a life crisis such as induction into the army, fear of combat, loss of loved ones, and the like. Furthermore, all patients with a history of mental deficiency, psychogenic or constitutional psychoses and organic disorders were excluded.

Eitinger and Laane stress the necessity of the psychiatrists themselves examining patients in order to obtain a reliable report of outcome. One hundred fifty-four cases were specially studied and classified by Langfeldt between 1940 and 1949. He divided them into 110 cases of schizophrenia and forty-four with schizophreniform symptoms. In the follow-up, made without knowledge of Langfeldt's diagnosis, it was found that in 105 cases the patients had continued to show symptoms of clear-cut schizophrenia and in only five had schizophreniform symptoms developed. Of the forty-four patients with schizophreniform symptoms thirty-nine continued in that category while five appeared to be schizophrenic on last examination.

This work of Langfeldt's is stressed here because it helps to explain the wide divergence of reported results of treatment of schizophrenic patients by various workers.

Langfeldt's work has not been widely accepted because few psychiatrists have had the time and the patience to select only the patients who clearly displayed the nuclear symptoms of Bleuler and, at the same time, exclude patients with complicating symptoms such as clouding of consciousness and marked emotional disturbances.

Mayer-Gross [*7*] has summarized the results of hospital care of schizophrenic subjects before shock treatments were introduced.

Many studies of hospitalized patients with chronic schizophrenia indicate that time alone makes it possible to select a group of schizophrenic subjects who resemble the Langfeldt group of true schizophrenics. Thus, patients who fail to have a remission during the first two years in the hospital may be expected to remain chronic schizophrenics in 50 per cent of cases. After five years 90 per cent or more will continue to have manifestations of schizophrenia [*7*, p. 267].

A large understaffed mental hospital for chronically ill patients may have 6.6 per cent remissions. A smaller hospital for acute cases may have remission rates over 50 per cent.

Most studies have been made on hospitalized patients with schizophrenia and we are just beginning to learn about ambulatory patients.

Hollingshead and Redlich [*8*] in New Haven found that schizophrenic patients in high socioeconomic classes who are treated as private patients rarely enter private mental hospitals. On the other hand, those from lower socioeconomic classes rarely receive outpatient treatment and are usually confined to state mental hospitals; and the majority become chronic schizophrenics.

It is also important to emphasize that schizophrenic symptoms arising in relation to a military setting usually have an outcome entirely different from those appearing in ordinary civilian life. Both in World War I and II these acute schizophrenic episodes were frequently observed but the symptoms usually disappeared on return to civilian life. Furthermore, they did not lead to an increase in the number of hospitalized patients with schizophrenia in any of the belligerent countries [*7*, p. 229].

These examples indicate the importance of knowing what group of schizophrenics one is working with and the setting in which they are cared for before undertaking research and attempting to evaluate the significance of reported discoveries.

INCIDENCE

There are approximately 750,000 patients in public mental hospitals and at least 400,000 of these are schizophrenics of the chronic type with slight chance of recovery. There is little reliable information concerning ambulatory patients with schizophrenia.

The prevalence of patients seeking treatment varies according to community, methods of survey, and ranges from five to eight patients per thousand population.

ETIOLOGY

Heredity and Schizophrenia. A considerable literature in Europe and Kallmann's work [*9*] in this country indicates that hereditary factors play an important part in the causation of schizophrenia.

The expectancy of schizophrenia developing in the average person is 0.8 per cent. In siblings of patients the frequency of schizophrenia is 7 per cent. According to Kallmann's data schizophrenia develops in 10 to 22 per cent of children of hospitalized schizophrenic patients. Kallman's careful studies of 953 twins demonstrate the important part that hereditary factors play in the production of schizophrenia. The rate of concordance for schizophrenia for 268 monozygotic twins was 86.2 per cent while for 686 dizygotic twins it was 14.5 per cent.

These rates are higher than those of other workers such as Slater and Rosanoff whose figures were 76 and 14 per cent and 67 and 10 per cent, respectively. The reasons for this are that Kallman spent much time in selecting cases and chose only those patients who had had the clearly defined nuclear symptoms of schizophrenia (the true schizophrenia of Langfeldt) for a number of years. The diagnosis also had been confirmed by other psychiatrists; and he did not hesitate to exclude patients with complicating symptoms or in whom the diagnosis was uncertain.

While most investigators agree on the decisive importance of hereditary factors in schizophrenia, the mode of transmittal of inheritance remains controversial and may best be left to the geneticists.

The data supporting the influence of genetic factors do not exclude environmental factors. They merely indicate that certain individuals, by virtue of heredity, are defective in some way that greatly increases their expectancy for schizophrenia.

There are two schools of thought concerning the principal factors leading to schizophrenia. One believes that psychosocial experiences are primary, the other that some somatic disorder accounts for schizophrenia. The convincing data indicating the importance of hereditary factors in schizophrenia make possible a partial reconciliation of the two points of view.

The psychodynamic point of view contends that genetically vulnerable people become schizophrenic because of failures in psychosocial development due to misadventures arising from maternal deprivation, traumatic sex experiences and unsolved conflicts of various kinds. Schizophrenia, therefore, can be prevented by providing a favorable family life and later psychosocial development. It is also contended that if patients are treated by psychotherapeutic methods early in the development of symptoms, when communication is still possible, progress of

the disorder can be arrested and in some instances reversed.

The school representing the somatic point of view contends that there is some genetically determined metabolic abnormality in patients with schizophrenia which renders them incapable of normal development under common life situations.

There is considerable evidence from clinical investigations suggesting that multiple factors are involved in the etiology of schizophrenia.

The psychodynamic school, led by the psychoanalysts, can point to a large number of reports of impressive recoveries of individual patients during psychotherapy. However these are usually patients in the acute phases of illness and with many of the characteristics suggesting that a good prognosis could be anticipated without treatment.

They also point to the acute schizophrenic psychoses following war and other disasters that clear up with restoration of normal life as demonstrating that adverse psychologic experiences produce symptoms of schizophrenia.

There is also the evidence summarized by Greenblatt, Hyde and co-workers [*10*] that changing from custodial care to a well run hospital with a therapeutic atmosphere results in an increased rate of recovery and a great reduction in the number of deteriorated catatonic and combative patients. Stanton and Schwartz [*11*] would go further and suggest that a psychoanalytically oriented program should further improve results. No data have appeared to support this latter contention, largely because the personnel and finances have not been available to develop this type of institution, to say nothing of evaluating results.

Even if workers concerned with psychosocial factors have not found the cause of schizophrenia, they have established the following important principles. Patients who can afford psychotherapy require admission to mental hospitals relatively rarely, while patients from lower economic classes receive practically no outpatient psychotherapy and only receive custodial care when symptoms require commitment to state hospitals. These people constitute the majority of the more than 400,000 patients with chronic schizophrenia in this country's mental hospitals.

A final important fact is that a well staffed hospital practicing modern milieu therapy obtains many more remissions and greatly ameliorates the symptoms of the majority of patients. There is little evidence, however, that this amelioration of symptoms actually can reduce the number of patients with schizophrenia.

The somatic school, in turn, is in the embarrassing position of having repeatedly discovered biochemical abnormalities, only to find out later that the discovery could not be confirmed or that non-schizophrenic control subjects had similar biochemical variations.

ATTEMPTS TO DEVELOP TESTS THAT WOULD AID IN DIFFERENTIATING SCHIZOPHRENIC PATIENTS FROM NON-SCHIZOPHRENIC SUBJECTS

Pyschological Investigations. The application of a wide variety of psychologic tests, such as the Stanford-Binet, Rorschach, TAT and many others has proved most unrewarding [*12*]. The difficulty lies in the fact that patients cooperate poorly, cover up queer ideas and yield little workable material.

Neurological Investigations. Neurological investigations [*13,14*] also have revealed variable but minor abnormalities. The most one can conclude is that schizophrenic patients manifest more abnormalities of response than control subjects but still these are not enough out of line to be of differential value.

Endocrine Investigations. The presence of endocrine abnormalities has been repeatedly discovered only to be disproved by later investigations. The thyroid, adrenals, testicles and ovaries have been most commonly implicated [*13,14*]. Manfred Bleuler [*15*], after years of work, finds no evidence of significant abnormalities of endocrine function in schizophrenic patients. The symposium [*16*] on psychoendocrinology at the Zurich Congress presented no evidence of endocrine abnormalities in schizophrenia.

Biochemical Investigations. The recent advances in biochemical genetics, and the development of sensitive technics of chromatography, of enzyme chemistry and of microchemistry have stimulated investigators throughout the Western World to renew the search for biochemical disorders in schizophrenic patients.

There have been a number of reviews and symposia that adequately cover this subject [*17,18*]. At the present time there is such a discrepancy between the reports of various workers that it is impossible to determine what, if any, biochemical abnormalities have been established in schizophrenic patients. A few illustrative examples will be reviewed.

At least fifteen investigators [*18*] have found various differences in the excretion of normal and abnormal compounds in the urine of schizophrenic patients. Among those most commonly found in abnormal amounts have been indoles, 5-hydroxyindoles, tryptophane metabolites and catechol amines and adrenaluetin. McGeer and McGeer [*19*] have recently published chromatograms of urine from schizophrenic subjects that differ strikingly from chromatograms of urine from non-schizophrenic subjects. According to Fabing [*18*], Sherwood has reported markedly increased excretion of indole acetic acid in the urine of schizophrenic patients. This apparently confirms similar findings of Ross in 1913.

Robins and Smith and associates [*20,21*] have attempted to confirm these numerous reports of abnormal substances in the urine of schizophrenic patients. They employed similar or recently improved chromatographic technics and found no consistent differences between patients with schizophrenia and control subjects.

The old problem of the difference between patients with chronic schizophrenia in a state hospital and schizophrenic patients in a well staffed university hospital may account for the differences. Robins and Smith in preliminary studies of patients in state hospitals found more abnormal chromatograms than in the schizophrenic patients in university hospitals. This work is still in progress and final conclusions are not warranted.

Biological tests of many kinds have also been employed by many investigators in the search for abnormal metabolites or toxic substances in the serum or urine from schizophrenic patients. There are many reports of positive findings that have not been confirmed.

Most recently Winter and Flataker [*22*], have found that the injection of extracts of urine from schizophrenic patients into climbing rats greatly depressed their climbing activity. Control substances did not have this effect. Heath and associates [*23*] at Tulane have done extensive work in this area, using monkeys and non-schizophrenic men as test subjects. In the process of extracting ceruloplasmin from serum obtained from various kinds of patients they obtained a fraction of unusual appearance in extracts of serum from patients with schizophrenia. Injection of this fraction into monkeys produced a stuporous state. The extracts that gave this reaction in the monkey were tested on volunteer men who were prisoners at the state prison. These tests were made under double-blind conditions. The extracts from schizophrenic patients produced catatonic symptoms while samples from control subjects did not. Robins and Smith [*24*] have repeated these experiments on volunteer prisoners in Missouri. They used extracts of serum generously supplied by Heath and his co-workers, and also extracts from the serum of schizophrenic patients and control subjects prepared in their own laboratory. In none of the subjects tested did symptoms develop as marked as those described by Heath. It is noteworthy that all but one subject complained of peculiar feelings and several were easily induced to hold up their arms in posture resembling catatonic patients. When the double-blind code was broken, no difference was found in the effects of extracts from schizophrenic patients compared with extracts from control subjects or physiological saline solution. As the number of subjects tested (fifteen) was small, this failure of confirmation may not be significant.

Deficiencies in diet apparently account for Akerfeldt's [*25*] finding that serum from schizophrenic patients oxidized N,N-dimethylparaphenylendiamine more rapidly than serum from control subjects. Attempts to confirm this finding revealed it to be related to the amount of ascorbic acid in the diet [*26*]. In fact, at the National Institute of Health where schizophrenic patients receive vitamin supplements the patients were even more normal in this respect than the control subjects who ate at home.

THE STATUS OF THE EMPIRICAL THERAPIES FOR SCHIZOPHRENIA

The literature reporting varying degrees of success in treating schizophrenic patients is enormous. Many recent reviews [*27–31*] are available and only special articles will be considered in this discussion. The wide conflict in results is easily understood, however, if we take into consideration the problems of diagnosis, prognosis and treatment already discussed.

It must also be remembered that schizophrenic patients are difficult to understand and to manage. They usually regress either into a vegetative state or one of unpredictable aggressive behavior if they are not especially cared for in a well staffed hospital.

It has just been rediscovered that sympathetic, adequate personal care in a hospital improves patient behavior and increases the number of

remissions. Greenblatt et al. [*10*] have recently reviewed these developments. In the 1840's reform and humane care pervaded the Massachusetts State Hospitals and discharge rates of new cases each year rose to 80 per cent or more.

The Civil War plus great waves of patients from deprived immigrant hordes entering the United States in the years after the war reduced the hospitals to understaffed prisons. The state mental hospitals in this country have never recovered from this post-Civil War era, although they have improved somewhat in recent years. Consequently, any new treatment that is introduced means that a great change occurs in the patient's environment. A previously neglected group of patients receives much attention and improved care and, as has repeatedly been demonstrated, a considerable number will improve from this effect alone.

Only a few of the numerous reported "cures" that later proved ephemeral will be discussed as examples.

In the period from 1929 to 1936 prolonged sleep was induced by many drugs, such as barbiturates and other long-acting anesthetics. Remissions were reported in 30 to 70 per cent of patients. It was usually noted, however, that patients in whom the onset was acute and of recent origin responded best and that patients with chronic states did not do so well.

The next apparently promising advance in treatment came with the insulin coma therapy of Sakal in 1933. Again, time and sober evaluation now suggest that insulin may be of value only in acute cases by shortening the duration of the first attack. For example, Appel [*27*] has compared the condition of patients treated with insulin with untreated patients after five years and has found no difference in outcome. Only 27 per cent of both groups were recovered or much improved.

Electroconvulsive therapy came next and is still used but recent follow-up studies reveal increasingly poor results. Freyhan [*32,33*] has reviewed results of treatment of schizophrenic patients in the Delaware State Hospital before and after introduction of electroshock therapy. He found a distribution of patients similar to Bleuler's, i.e., one-fourth recovered, one-half became chronic schizophrenics and one-fourth had frequent recoveries and remissions. After the introduction of shock therapy, however, a more rapid discharge rate of new cases was apparent but 50 per cent continued to become chronic schizophrenics.

The results obtained from the treatment of patients selected by Langfeldt as being true schizophrenics with a poor prognosis will now be considered.

Eitinger and Laane [*6*] found that ninety-two of the 105 schizophrenic patients selected by Langfeldt ten to fifteen years previously remained unchanged or worse, regardless of treatment previous to time of follow-up. Only five were able to work and, on the whole, were free of symptoms. Noteworthy are twenty of the 105 patients who received no electroshock therapy or insulin coma or other somatic therapy. Only one of these patients had recovered, three were somewhat improved. These authors conclude that present day methods of treating schizophrenia (i.e., convulsive therapy or hospital care) are completely inadequate.

In contrast to the true schizophrenics, it was found that in thirty of thirty-nine schizophreniform cases the patient had recovered, the majority (twenty-four) of these following electroconvulsive therapy. The authors regret the lack of an adequate control group for comparison. Only six received no special treatment; two recovered and four showed some improvement.

We can therefore conclude that before the advent of tranquilizing drugs neither electroshock nor insulin therapy had much effect on the outcome of chronic schizophrenia. When all the groups of the schizophrenias are included, there is some evidence that the first symptoms can be alleviated by electric shock treatment or insulin coma and the time spent in hospitals greatly reduced but the ultimate outcome remains unchanged.

The new tranquilizing drugs, chlorpromazine and reserpine, were introduced as treatment for schizophrenic patients in 1952 in France and in 1953 in India, respectively. They have proved enormously popular and the literature describing therapeutic success is overwhelming in amount but largely uncritical.

Again we have the old story, the understaffed state hospitals take up the new drug with enthusiasm, patients improve and are discharged. However, the present results appear much more impressive than those for any previous treatment. More patients have improved sufficiently to be discharged than ever before and many are able to get along at home if the drug is continued.

The results have been evaluated for the New York State hospitals by Brill and Patton [*34*]. The drugs were introduced on a large scale late in 1955. For the first time, except for two war years, more patients were discharged in 1956 and 1957 than were admitted. The most favorable results were obtained in the schizophrenias. Furthermore, fewer patients were readmitted. Before the advent of these drugs the annual increase in patients in New York State Hospitals had been rising steadily for many years and by 1955 was 2,421. This process was reversed in 1956 when there was a decrease in patients of 452 and again of 453 in 1957.

These figures should be interpreted with caution, however, because, as with previous therapies, most of the improvement occurs in new cases, and little change occurs in the patients with chronic schizophrenia, i.e., patients who had been in the hospital for two or more years. But even in the patients with chronic schizophrenia there was a marked improvement in ward behavior. Disturbed behavior was reduced and restraints and seclusion were no longer needed. Similar reports come from all over the country.

In contrast with the experience of the large public hospitals, the reports from the smaller well staffed university hospitals and the private hospitals are not so glowing. The administration of chlorpromazine has proved helpful in controlling over-activity and aggessive behavior, and patients seem more comfortable, but very few were relieved of their main schizophrenic symptoms. In discussing Brill and Patton's paper [*34*], Eisen reported that at Michael Reese and other private hospitals the results of treatment "failed to show the cure rates reported in other studies." A number of controlled studies [*28,30*] and double-blind studies [*35*] suggest that chlorpromazine after all may not be much more effective than the barbiturates or the placebo in alleviating schizophrenic symptoms.

It seems proper to conclude that chlorpromazine and other phenothiazine derivatives alleviate schizophrenic symptoms and make patients easier to manage but probably do not alter the course of the disorder.

CONCLUSIONS

The designation schizophrenia includes groups of patients with disorders in thinking and behavior that render them asocial and difficult to care for. They have overcrowded the hospitals in increasing numbers and, with the exception of senile disorders, constitute the largest group of mentally ill patients.

Research has been hampered by inadequate hospitals and staff, by failure to discriminate among the different groups of patients and, particularly, by failure to separate acute from chronic cases and those with good prognosis from those with poor prognosis when evaluating results of research or therapy.

There is ample evidence that schizophrenia is a genetically determined disorder. It is therefore reasonable to expect that there must be some metabolic defect in schizophrenic patients. Failure in the past to discover one or more metabolic abnormalities has been due to poor research design and inadequate methods. Application of the new and delicate technics of investigation now becoming available to the study of specially selected schizophrenic patients in a controlled evironment may ultimately yield significant results.

It is noteworthy that there are many preliminary reports of positive findings but none as yet have been adequately substantiated by other investigators.

While we are awaiting the discovery of the metabolic abnormality it should not be forgotten that there is good evidence that early treatment with psychotherapy [*8,36*] can at least greatly alleviate symptoms so that hospital care may not be necessary for years. There is therefore the prospect that the number of schizophrenic patients in hospitals could be reduced by early psychotherapy and, if necessary, treatment is adequately staffed hospitals.

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Clinico-pathological Conference

Multiple Thrombotic Episodes with Death Following a Reaction to Miokon

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A WHITE male pipe worker, fifty-five years of age, from Ozark, Missouri, was admitted to Barnes Hospital for the first time on March 19, 1958. He died on March 22, 1958 following a reaction to the intravenous administration of Miokon.®

The patient had been in good health until three or four months prior to admission when he injured his left shin and an ecchymosis developed which lasted for one week. About eight weeks prior to admission he had injured his left knee in a fall following which he had had tenderness but no swelling or ecchymoses. One week later his right calf became painful and swollen with increased heat and possible redness; this lasted for one week and disappeared without residum. The left calf then became involved in a similar manner and a week later the left forearm became swollen with the appearance of a hard inflamed vein along the medial aspect near the elbow. Following this in succession, the right ankle, the lower part of the left leg and the right and left buttock became swollen, tender, and moderately inflamed, each lasted about a week before clearing. In spite of therapy with dicumarol a similar process developed in the lower part of the right leg and later in the right antecubital area. During most of these episodes a tender venous cord could be palpated. Pain in the legs was so intense that the patient was unable to walk, and he received only slight relief from sedatives. Three weeks prior to admission he had been admitted to a hospital in Springfield, Missouri. Physical examination at that time revealed tender hard, red veins in the buttocks and legs. Arterial pulsations were present and there was no cyanosis of the extremities. The blood hematocrit was 49 per cent, the hemoglobin was 16 gm./100 ml., and the white blood cell count was 9,150/cu. mm. with a normal leukocytic pattern. The sedimentation rate was 48 mm./hour. The cardiolipin reaction for syphilis was negative. The platelet count was 130,000/cu. mm. The bleeding time was one minute and the clotting time was three minutes and five seconds. A glucose tolerance test revealed a diabetic type curve with a fasting blood sugar of 100 and a three hour sugar of 125 mg./100 ml. Liver function studies including bromsulphalein retention, alkaline phosphatase, total and fractional proteins, bilirubin and flocculation studies were all within normal limits. The serum uric acid was 4 mg./100 ml. The antistreptolysin titer and C-reactive protein were normal. Agglutinins were reported negative (type not specified). A chest roentgenogram was normal and an upper gastrointestinal series showed a normal stomach; however, the duodenal loop was not seen clearly on any film. A barium enema was considered to be normal. Bone marrow examination showed "hyperplasia with megakaryocytosis." The blood was noted to clot readily; however, at six hours only a fragile clot was present with loose red blood cells at the bottom of the tube. The one stage "prothrombin" level was 33 per cent. A muscle biopsy specimen revealed "thrombotic arteritis." The patient was treated for five days with heparin, dicumarol, phenobarbital and Priscoline®; morphine sulfate was given for relief of pain. He showed no improvement and was transferred to Barnes Hospital for further evaluation.

The patient gave no history of previous cardiovascular disease. He denied chest pain, dyspnea, shortness of breath, and hemoptysis.

There was no weight loss, abdominal or back pain, nausea or vomiting, melena or bloody stools. Prior to the onset of his illness he had not noted plethora or easy bruising. There were no varicosities, Raynaud's phenomena, or ulceration of his fingers or toes. He had smoked until two weeks prior to admission when he was advised by his physician to stop. There was no history of a similar illness in any member of his family or relatives.

The patient had had an appendectomy in 1934. There was a history suggestive of peptic ulcer twenty years prior to admission but he had had no gastrointestinal symptoms for the last ten years. One testicle had been injured when he was twelve years old.

The patient's mother died at age sixty-nine of heart trouble; his father died at age seventy-five of carcinoma of the kidney. He had five brothers and one sister all living and well. One daughter was reported to have "platelet trouble" with menstrual irregularities but her last blood count was within normal limits.

The physical examination was as follows: blood pressure, 137/80 mm. Hg; pulse, 84/minute; respirations, 20/minute; temperature, 37°c. The patient was well nourished and appeared in no acute distress. There were no petechiae, ecchymoses or other abnormalities of the skin. A few small shotty lymph nodes were palpable in the cervical and inguinal areas. The optic fundi were normal. The lungs were normal to percussion and auscultation. The heart was normal. The second aortic sound equalled in intensity the second pulmonic sound. There was no tenderness of the abdomen; the liver was palpable 4 cm. below the right costal margin. The spleen and kidneys were not palpable; no masses were noted and the bowel sounds were normal. The right testis was absent and there was an enlarged inguinal ring. Arterial pulsations were good in all extremities except for the right ulnar artery. There was 4-plus edema of the right leg extending to the knee. Homans' sign was present on the right and possibly on the left. The calf of the right leg was indurated and tender with palpable cords extending to the popliteal space. There were hard palpable cords in the left calf, and tender palpable cords in the left forearm along the left ulnar border, in the antecubital fossa, and along the course of the brachial artery. There was no definitely increased heat or tenderness of the right leg. The neurological examination was within normal limits and deep tendon reflexes were bilaterally present and equal.

The laboratory data were as follows: hematocrit, 40 per cent; white blood cell count, 9,700 per cu. mm.; with a differential of 2 eosinophils, 1 band, 66 polymorphonuclear leukocytes, 28 lymphocytes and 3 monocytes. The platelet count was 300,000/cu. mm. The sedimentation rate was 21 mm./hour (uncorrected). The stained peripheral blood film showed normochromic and normocytic red blood cells, and large abnormal platelets which appeared greatly increased in number. Urinalysis was normal with a specific gravity of 1.022. The blood cardiolipin reaction was negative. The non-protein nitrogen was 23 mg./100 ml.; fasting blood sugar, 88 mg./100 ml.; total serum protein, 6.1 gm./100 ml.; with an albumin/globulin ratio of 3.5/2.6; alkaline phosphatase, 4.5 Bodansky units; acid phosphatase, 1.5 units; uric acid, 4.3 mg./100 ml.; phosphorus, 3.6 mg./100 ml.; amylase, 62 units; serum glutamic-oxalacetic transaminase, 22 units; and serum glutamic-pyruvic transaminase, 12 units. Serum electrolyte values were normal. The cephalin-cholesterol flocculation was 1 plus; thymol turbidity, 0.4 unit; total serum bilirubin, less than 0.8 mg./100 ml.; and cholesterol, 139 mg./100 ml. The serum electrophoretic pattern was normal. The roentgenograms from the other hospital were reviewed and interpretation was as previously recorded. Aspirated bone marrow showed a slight increase in eosinophils and an apparent increase in megakaryocytes, but was otherwise unrevealing. An electrocardiogram revealed low voltage in the standard leads and was otherwise normal. The clotting time was twenty minutes and the prothrombin time was 52 per cent.

The patient was treated with dicumarol and heparin, the clotting time being checked every six hours. It was noted that the patient's blood clotted readily but the clot was not firm, and numerous red blood cells fell to the bottom of the tube. Compression of the ulnar-radial artery at the right wrist with blanching of the hand produced by exercise showed no relief of blanching when the ulnar artery was released (Allen test). This was interpreted as compatible with right ulnar artery thrombosis. Oscillometric studies were generally diminished in all extremities. On the third hospital day, the patient was sent to the Radiology Department for intravenous pyelograms and received 1 cc. of 50 per cent Miokon which was followed one minute later

by an additional 25 cc. Some extravasation occurred and a second venipuncture was necessary to complete the injection. During the injection the patient complained of a sensation of pins and needles with some pruritis but no urticaria. The injection was stopped immediately and 20 mg. of Benadryl® were given intravenously. The patient continued to feel ill but his pulse was noted to be normal and full. A five-minute film showed a nephrogram and this was subsequently interpreted as being compatible with hypotension. The patient's blood pressure was found to be 60/40 mm. Hg; he was immediately given Vasoxyl® intramuscularly, norepinephrine intravenously, and oxygen by mask. After two hours, it was necessary to administer increasing amounts of norepinephrine to maintain his blood pressure. Three hours after injection he began to complain of chest pain, and vomited blood. An electrocardiogram showed changes compatible with a recent anterior myocardial infarction, anterolateral subendocardial myocardial injury, frequent ventricular premature contractions, sinus tachycardia, and some prolongation of conduction. During the succeeding four hours he required the administration of still more norepinephrine and hydrocortisone to maintain his blood pressure at 120 mm. Hg (systolic). Six hours after injection the patient became clammy. He was irrational and thrashed about in bed. He again vomited blood. In spite of the administration of increasing amounts of norepinephrine he gradually became unresponsive, lapsed into coma with dilated pupils, and died. A roentgenogram of the abdomen taken two hours after injection of the Miokon still showed the nephrogram. During the terminal episode the patient received 158 ampules of norepinephrine, 4,000 ml. of 5 per cent glucose in water, 70 mg. Benadryl, 400 mg. hydrocortisone, 1 unit of plasma, 1 unit of whole blood, heparin, morphine and Demerol.®

CLINICAL DISCUSSION

DR. EDWARD REINHARD: Let us first consider the etiology of this patient's thrombotic disorder, and determine whether or not vascular thrombosis involved the veins, the arteries or both. It certainly would seem likely that there was thrombophlebitis in the legs in that marked edema of the right leg developed. The positive Allen test in the right arm was interpreted to mean right ulnar artery occlusion. A muscle biopsy specimen obtained in a hospital in Springfield showed "thrombotic arteritis involving the small arteries in the muscle." Dr. Goldman, would you agree on the basis of this information that the patient had both venous and arterial thromboses?

DR. MELVIN GOLDMAN: I suspect that he had both venous and arterial thromboses but there is some question regarding the timing of these. On the basis of the available clinical evidence one would say that there had not been a recent arterial occlusion of any major vessel. Certainly there were signs and symptoms of recent thrombophlebitis but the extremities were not cold. The thrombosis in the ulnar artery may have been an older event, possibly unrelated to the present episode.

DR. REINHARD: How do you interpret the report of a thrombotic arteritis?

DR. GOLDMAN: We have to accept that. He may certainly have had involvement of smaller arteries.

DR. REINHARD: Dr. Thomas, is it possible that a thrombus in a vessel might produce reaction in the wall of the vessel that could be interpreted as an arteritis?

DR. WILBUR THOMAS: Yes.

DR. REINHARD: Dr. Sherry, do you think this patient had a generaiized arterial disease such as periarteritis?

DR. SOL SHERRY: If the patient had thrombosis on the arterial as well as the venous side, there could well have been some underlying vasculitis to account for the multiple thrombotic episodes.

DR. REINHARD: There is certainly nothing that suggests a true periarteritis, is there?

DR. SHERRY: No.

DR. REINHARD: Dr. Goldman, thromboangiitis obliterans was one of several possible diagnoses suspected.

DR. GOLDMAN: Buerger's disease or thromboangiitis obliterans in our experience is a very rare disease. Since the advent of angiography and other means of studying vascular disease, many cases that we previously thought were Buerger's disease have not met the necessary criteria. In other words, many younger persons who present with obstruction of blood vessels show the angiographic findings and pathologic condition of arteriosclerosis. I do not think this patient had either the signs or symptoms of Buerger's disease. Usually in Buerger's disease, segmental and inflammatory disease of the vessel is found, which lead ultimately to gan-

grene. There is no evidence in this patient that he had gangrene in any of the extremities.

DR. REINHARD: I would certainly agree. Let me direct your attention now to a consideration of the underlying cause of this patient's obvious thrombotic disease. There are four major possibilities: (1) that the patient might have had primary vascular disease, (2) that he might have had a primary coagulation abnormality of some sort and thromboses developed because of a hypercoagulability of the blood, (3) that he might have had cancer, and (4) that he may have had multiple thromboses without obvious cause. Before we leave the first category, is there anyone who wishes to defend primary vascular disease as a likely possibility?

DR. SHERRY: I still think it is likely. I do not know how to defend it any further, except that in my own mind the best explanation for multiple thromboses both on the arterial and venous side, would be some alteration in the endothelium of vessels, providing a likely site for thrombosis. We have no evidence that there are any primary coagulation abnormalities present in this patient. In cases of neoplasia one would tend to see thrombophlebitis, but I do not know of any arterial thrombi under those circumstances.

DR. REINHARD: Let us now discuss the possibility of a coagulation abnormality underlying the thrombotic disturbance. Dr. Harrington, would you mention the primary hematologic disorders that are known to give a predilection to thrombosis?

DR. WILLIAM HARRINGTON: There are two categories of disease fairly often encountered. In the first a high platelet count is featured, and in the second hemolysis.

Chronic granulocytic leukemia and polycythemia vera are the most common underlying disorders accompanied by thrombocytosis. The postsplenectomy state may present a similar problem. At times other processes, e.g., severe iron deficiency anemia, myeloid metaplasia, and essential thrombocytosis (a rare disease), are responsible. Other factors, especially an increase in viscosity of the blood as in polycythemia, undoubtedly compound the probability of intravascular coagulation.

Among the hemolytic diseases, paroxysmal nocturnal hemoglobinuria is especially noted for thrombotic complications. Perhaps the chronicity and severity of the hemolytic episodes determine this characteristic. Hemoglobinopathies, especially of the S and C varieties, often present serious complications due to thromboses.

Less common causes with hematologic aspects include the dysproteinemias (cryoglobulinemia, cryofibrinogenemia, and extreme degrees of hyperglobulinemia), essential thrombophilia (a disorder of elusive pathogenesis, diagnosed by exclusion), and the distressing tendency for thrombosis to develop in patients with deficiency anemias during an otherwise pleasing response to specific therapy.

DR. REINHARD: Dr. Moore, can we dismiss all these possibilities?

DR. C. V. MOORE: There is nothing to suggest that any was present.

DR. REINHARD: Now we come to a consideration of an underlying neoplasm. Dr. Tombridge, would you briefly comment on the evidence that cancer of the pancreas or of other organs may predispose to thrombosis?

DR. THOMAS TOMBRIDGE: It seems rather well established in the literature that there is such a relationship. The first report I came across in the American literature was that by Sproule in 1938. This and most of the earlier reports concerned carcinoma of the pancreas, particularly carcinoma of the body and tail of the pancreas. Since that time carcinomas of many visceral organs, particularly carcinoma of the lung and stomach have been implicated. This type of thrombophlebitis is resistant to anticoagulation therapy. Some people are apparently so convinced of the relationship that they will subject any person over the age of thirty with anticoagulant-resistant thrombophlebitis to abdominal exploration even though there is no other evidence of visceral or pancreatic carcinoma.

DR. REINHARD: Dr. Moore, are you entirely convinced that the incidence of multiple thrombosis, even when the thrombosis appears to be anticoagulant resistant, occurs more frequently in association with carcinoma? Could this be just a chance or coincidental association of two fairly common disorders?

DR. MOORE: While there are some dissenting opinions, most of the people who have studied the problem are convinced that the incidence of multiple thromboses in patients with carcinomas of the pancreas, lung and stomach is greater than would occur by chance alone.

DR. REINHARD: Dr. Sherry do you know of any theoretical mechanisms by which cancer could predispose to multiple, extensive migratory thrombosis?

DR. SHERRY: The formation of a thrombus depends on a balance between the rate of fibrin formation and the rate of its dissipation by a rapidly moving circulation. Under ordinary circumstances blood clots slowly in normal vessels and significant thrombus formation does not occur. Factors accelerating thrombus formation would include an abnormal or inflamed surface, release of thromboplastic substances into the blood, or a significant slowing of the circulation. Furthermore, it is conceivable that in the presence of depressed fibrinolytic mechanisms small thrombi may not be disposed of and may develop into clinically significant ones. At present, I favor the view that malignant tissue releases thromboplastic substances into the blood stream, enhancing the tendency toward coagulation.

DR. HARRINGTON: In any chronic wasting disease the pathologist may find deposition of fibrin in many sites, including the heart valves. These aseptic fibrinous deposits could presumably lead to embolization. Such a process might account for some of our patient's symptomatology.

DR. GOLDMAN: Dr. Reinhard, our experience in abdominal exploration for a possible source of neoplasm in idiopathic thrombosis has been very disappointing. Nevertheless, it must often be performed. Usually in older patients with far advanced cancer the relationship to thrombosis is much more obvious than in younger, apparently healthy persons presenting with idiopathic thrombophlebitis.

DR. REINHARD: The last diagnostic category which deserves some comment must now be considered: extensive migratory thrombophlebitis without any evidence of blood disease, primary vascular disease or carcinoma. Dr. Perry has such a patient in the hospital now. Perhaps he could tell us about postmortem findings in reported cases.

DR. WILLIAM PERRY: The largest series I have found was that of Parker at the Mayo Clinic. He studied several of these cases many years ago. In some instances these patients, for many years prior to development of phlebitis, noted transient little blue bumps on their arms along the course of the veins. I went back to ask my patient about this and sure enough he has had little blue tender spots along the course of his veins for some twenty years. His mother also had this type of illness. I do not know how to interpret this. It is interesting that these patients are also resistent to anticoagulants.

DR. REINHARD: Dr. Thomas are you familiar with the pathologic counterpart of these blue bumps?

DR. WILBUR THOMAS: No.

DR. REINHARD: I would like to mention just one last case in passing. A young girl in her teens was a patient at Barnes Hospital just recently. She presented with thrombophlebitis in her left leg. While receiving anticoagulant therapy, a very severe headache developed which was thought to be due to a cavernous sinus thrombosis. Postmortem examination disclosed extensive thrombosis involving the veins of her extremities, the ascending veins from the lower extremities and also the brain. There was no evidence of cancer or vascular disease.

DR. M. GOLDMAN: Dr. Reinhard, may I add another word or two about this group of patients? There are certain other findings which I think are characteristic. These patients do not tolerate procedures very well. For example, in two of them we may have precipitated thrombosed arteries with intra-arterial histamine treatment. At the time we did not know why thromboses occurred. Thromboses seem to form more readily in these patients than in other people. Dr. E. V. Allen, I think, refers to this group of people as having "thrombosing" disease.

DR. REINHARD: I think we have established the point that certainly there are patients who have extensive multiple migratory thromboses for which no cause is known at the present time.

The cause of death in this patient should now be considered. The report describing the Miokon reaction reads in part as follows: "This patient was referred to radiology for intravenous pyelography. He gave no history of allergy and was normotensive. He received an initial intravenous test dose of 1 cc. of 50 per cent Miokon. After one minute, during which time the patient exhibited no reaction, the injection was continued." Dr. Nicolai, is this type of test really a worthwhile procedure? Can you avoid reactions by a one-minute wait?

DR. CHARLES NICOLAI: Admittedly there is no good pretesting procedure. The many different routes tested have all proved to be inadequate: sublingual, intraocular, subcutaneous, intracutaneous, intravenous, etc. The intravenous test is probably the easiest for us to perform and perhaps is as good as any. In other words, we

have gone through a testing procedure that is admittedly inadequate.

DR. REINHARD: How often is the pyelographic examination cancelled because the patient does have a reaction within one minute to the injection?

DR. NICOLAI: In the past five years I have not witnessed one.

DR. REINHARD: After the initial test dose of 1 cc. was given, the patient had no apparent reaction. "However after injection of 5 or 6 cc. in the right antecubital vein, some infiltration was noted and the injection was discontinued. The patient complained of local pain in the region of extravasation. Another venipuncture was made. The contrast medium was then slowly injected and after about 20 to 25 cc. of material had been injected, the patient began to complain of pins and needles sensations with some itching. There were no skin manifestations. The injection was stopped after 25 cc. had been given. The patient was given 20 mg. of Benadryl intravenously. Resolution of the itching complaints followed shortly thereafter." I will not read the rest of this report since you are familiar with the facts that the patient did become hypotensive, was given oxygen, Vasoxyl, plasma, whole blood, etc. Dr. Humphrey, would you show us the pyelograms which caused so much trouble?

DR. HARVEY A. HUMPHREY: Abdominal films exposed sporadically during the two hour interval after the reaction revealed: (1) bilateral nephrograms with concentration of dye in the kidneys and (2) lack of visualization of the calyces, pelves, ureters and bladder. These observations are understandable and to be expected in the presence of systemic arterial hypotension. Relevant to the patient's presenting disease is the fact that the left kidney was in a lower position than the right kidney, a common finding in carcinoma of the tail and body of the pancreas. This downward displacement of the left kidney and the resultant discrepancy in the relative positions of the two kidneys was more apparent on the films exposed at the end of inspiration (when the diaphragm was in a lower position) than on the films exposed at the end of expiration. Due to the subsequent chain of events the indicated examination of the gastrointestinal tract was never accomplished.

DR. REINHARD: Dr. Walsh, before we go on, I would like to consider the electrocardiographic findings. This patient had an electrocardiogram taken two days before the pyelograms were obtained and two records were obtained following the apparent Miokon reaction. Would you tell us what they showed and whether or not you think the patient had a myocardial infarction?

DR. THOMAS WALSH: The first record was within normal limits. There was a tendency to low QRS voltage which probably represented a normal variation. The second record, obtained shortly after onset of the apparent reaction to Miokon, showed rather striking changes. There was QRS interval prolongation (0.11 seconds) together with other evidence of an intraventricular conduction disturbance and T wave abnormalities. The appearance of depressed ST segments in the left precordial leads was indicative of subendocardial myocardial injury. The low R waves or QS waves in V2 and V3 were interpreted as being suggestive of recent anterior myocardial infarction. Although it was quite correct in view of these QRS changes to raise the question of infarction, the absence of elevated ST segments in these leads and deeply symmetrically inverted T waves would tend to implicate positional changes or changes related to the intraventricular conduction disturbance itself. Certainly the third electrocardiogram recorded several hours later showed nothing to suggest anterior infarction, so that I would consider myocardial infarction an unlikely diagnostic possibility.

DR. REINHARD: Dr. Smith, the protocol states that this patient vomited blood, but in going over the hospital record, I noticed that the intern's notes specifically say that the patient vomited and coughed about 100 cc. of gross blood. We know that if a patient is bleeding from the lung he may swallow blood. It is sometimes very difficult or even impossible to be certain whether blood is coming from the lung or from the stomach. Do you think there is any possibility that this patient had a pulmonary embolus?

DR. JOHN SMITH: Yes, that could well have happened. Sometimes hemorrhage from pulmonary embolism or from the formation of a pulmonary infarct after the embolism has occurred can be fairly copious. Usually, however, there are collateral symptoms in the way of cough, struggle for breath, and a distressing type of dyspnea that goes with it. This is not the usual clinical picture of pulmonary embolism with in-

farction and I would be inclined to doubt that the lesion was present here.

DR. REINHARD: What do you think accounts for the bleeding?

DR. SMITH: This patient went into a very serious shock-like state and one would assume that this was similar to an anaphylactoid or neurogenic type of shock. In these instances both the arterioles and the venules are dilated and absorb quite a lot of the circulating blood volume. Now, if there were a tendency to multiple thromboses throughout the body or if there were a lesion of some sort within the stomach, whether it be carcinoma, a thrombotic type of lesion or an ulcer, such as dilatation of vessels might lead to rather brisk bleeding.

DR. REINHARD: Now we would like to discuss Miokon reactions. Dr. Nicolai published several papers on these pyelographic media and I have asked him to begin this discussion.

DR. NICOLAI: These media have been developed in the last twenty to thirty years. It was not until compounds such as diodrast and Neo-iopax® came along that intravenous urography really found its place. These compounds are iodine-containing organic materials. The parent compound of the group is Urokon,® a triiodinated ring with an asymetrical side chain attached. Hypaque® differs in that it has a symmetrical radical. Miokon has two CH_3 groups. Renographin,® with which we have had little experience here, is a combination of both a sodium salt and a methylglucomine which increases the solubility of Urokon. The high percentage of iodine in Urokon has permitted a tremendous increase in the opacification of the excreted medium.

Since we were interested in studying reactions to these compounds, we followed a series of 1,500 cases in which we had a "double blind" method of administration of Neo-iopax, Hypaque and Miokon. We gave these compounds under standard conditions and, excluding pain in the arm which is due to venous irritation with the Neo-iopax, there was no significant difference in reaction rate among these compounds. The reaction rate for all compounds was between 12 and 13 per cent, including nausea, vomiting, flush reactions, tingling, the "feeling funny all over," hypersalivation and dermatitis. The important question is what to do about reactions. We have, as is recommended by many workers in this field, a complete kit of emergency medications on hand; a thoracotomy set nearby, and a ready communication pathway to the Chest Service. Prompt institution of emergency measures, including cardiac massage may occasionally be necessary if the patient is to survive.

DR. REINHARD: Dr. Eisen, I wonder if you would discuss the pathogenesis of the shock-like syndrome encountered with these contrast media?

DR. HERMAN EISEN: I would like to discuss two possibilities: (1) that these responses are allergic reactions to the iodinated compounds, i.e., that they are mediated by antibodies specifically complementary to Miokon and related iodinated benzenes; and (2) that the responses are not allergic, but rather directly due to histamine liberation.

With respect to the possibility that these reactions are allergic, one must ask first whether or not the responses are inducible and specific. Dr. Nicolai assures me that persons who receive a series of Miokon injections for pyelography are not more likely to have shock-like or other reactions after the later injection than after the first injection. The incidence of reactions does not increase with increasing numbers of Miokon injections. Moreover, Dr. Nicolai tells me that urologists have not encountered serum sickness-like syndromes developing anywhere from three to fourteen days after injections of Miokon. There are, in other words, no clinical indications that the common reactions to Miokon are inducible. In addition to their being induced, allergic reactions are specific. In respect to the specificity of Miokon reactions clinical information is lacking because patients who have suffered reactions to Miokon are not ordinarily re-injected with this or with structurally closely related materials. In any event the available clinical experience does not support the notion that common reactions to Miokon are mediated by antibodies.

From more general considerations one has to consider whether Miokon and related iodinated compounds are protein reagents, i.e., whether or not they react with proteins to form stable protein conjugates. This question must be asked because it is known that for simple substances to induce the sensitized state or to elicit the allergic reaction in the already sensitized host, it is necessary that the simple substance form stable conjugates with proteins. Miokon itself, I would judge, is incapable of forming the necessary kind of stable protein conjugate. I understand that Miokon is bound reversibly by serum

albumin. Such reversible binding by protein does not, however, furnish protein complexes with sufficient stability for biologic activity in immune and allergic systems. One must of course consider the possibility that there are contaminants in Miokon which are protein reagents. For pyelography enormous quantities of radiopaque dyes are injected, e.g., 12 to 13 gm. of Miokon. From our experience with other simple chemical sensitizers we would expect that generalized allergic reactions could be obtained with 1 mg. or possibly even 100 μg. of a potent low molecular weight sensitizer. Consequently, a contaminant present in Miokon to the extent of about 1 part of 12,000 (and possibly much less) could be responsible for the reactions under discussion. Contamination at this level would escape detection by conventional analytical methods. In considering possible contaminants one ordinarily looks at the procedures used to synthesize the bulk compound under discussion. According to the process used to synthesize Miokon, the possible contaminants which might be present are: (1) the non-acylated substance, i.e., 3, 5-diamino 2,4,6-triiodobenzoate or (2) a diiodo instead of the triiodo substance. I would not expect either of these two possible impurities to be any more of a protein reagent (sensitizer) than is Miokon itself. Is it possible that Miokon is subject to rapid metabolic alterations yielding products which are capable of reacting with proteins to make stable conjugates? I do not know the answer to this question, but it seems an unlikely possibility to account for the very rapid shock-like response under discussion. From all these considerations I am skeptical that the shock-like responses to Miokon are allergic reactions.

I would like to raise the question that the reaction is due to the direct action of Miokon (or possible contaminants in it) on mast cells with resultant massive release of histamine. Dr. Helen Graham informed me yesterday that most of the simple histamine liberators are characterized by their having strongly basic amino groups. Presumably these compete with histamine for cell-bound anionic groups in mast cells and displace histamine from such receptors. Miokon itself would be a rather weak basic substance, and even 3,5-diaminotriiodobenzoate would be a weak base. On this account, Miokon might not be expected, perhaps, to be a potent histamine liberator. There are, however, many other factors involved in histamine liberation. For example, non-ionic dextrans are histamine liberators, and it is possible that Miokon, etc., cause massive release of histamine. In view of the important recent developments in histamine measurement, I should think it would be feasible and desirable to determine whether or not massive histamine liberation occurs in those human subjects in whom shock-like responses to Miokon develop.

DR. REINHARD: I would like to discuss the therapy of this type of reaction. There is a notice posted in the Radiology Department which serves as a constant reminder of the steps which should be taken, should a severe hypotensive reaction occur. The person performing the pyelographic examination is instructed to notify the patient's physician and the resident immediately. The Department of Anesthesiology is to be informed immediatedly. The nurse who assists in cystoscopy is instructed to bring to the room immediately the emergency medication kit, thoracotomy set, syringes, needles and so on. The emergency treatment to be given is then outlined. The Department of Anesthesiology will give oxygen if indicated. Intravenous medications available include Benadryl, ephedrine and cortisone. For the hypotensive aspects of this type of reaction, ephedrine may be used, and Vasoxyl may be required. Intracardiac calcium chloride might be indicated for cardiac arrest. The last item on this notice is a warning against the use of respiratory stimulants as these may induce convulsion.

In conclusion, the final diagnoses I would like to present are: multiple, arterial and venous thrombi due to in order of likelihood (1) cancer, (2) no demonstrable cause and (3) primary vascular disease. I think we can be almost certain that there was no hemotologic disorder. I think the patient certainly had a reaction to Miokon producing a shock-like state, and I am inclined to think that during the post-Miokon shock-like state that the patient had a pulmonary embolus, which was the actual cause of death.

PATHOLOGICAL DISCUSSION

DR. TAN TEK TJIEN: At autopsy, this well developed and well nourished elderly white man showed marked edema of the lower extremities. Cord-like structures could be felt in both the lower and upper extremities. On further examination of the legs, multiple thrombi were found occluding the lumens of the femoral, saphenous and small pedal veins. On opening the thorax

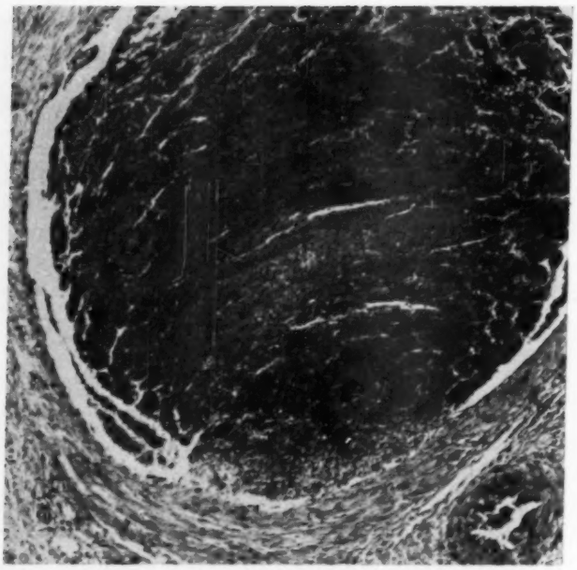


FIG. 1. A large laminated thrombus in a branch of the femoral vein, typical of those found in both legs. A point of attachment and beginning organization is present in the lower center. Hematoxylin and eosin × 45.

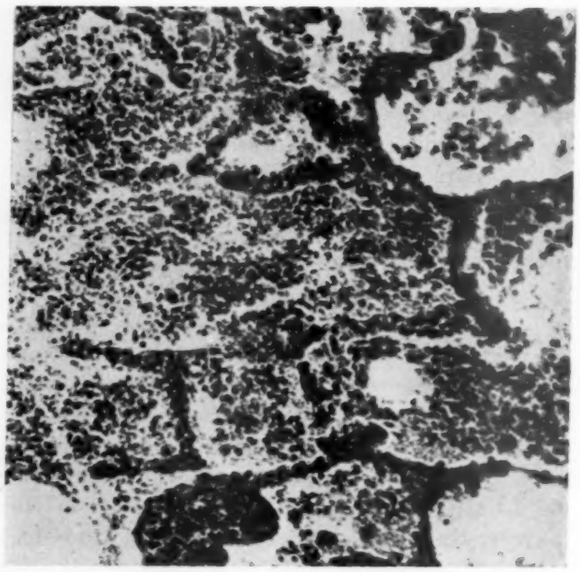


FIG. 2. Marked hemorrhage into alveoli and congestion of alveolar walls in the area of "incomplete infarction" of the upper left lobe. Hematoxylin and eosin × 100.

100 ml. of serosanguinous fluid were found in the pleural cavity. The lungs weighed 1,350 gm. and appeared congested and edematous. There were pleural adhesions and multiple emphysematous areas in the apexes of the upper lobes. The upper lobe of the left lung showed also a large triangular hemorrhagic area. Further examination of the lungs revealed friable red thrombi in the medium-sized branches of the pulmonary artery of the upper left lobe. The heart weighed 450 gm. and appeared dilated and hypertrophied, especially the left ventricle. The pancreas was huge, firm and grey and weighed 180 gm. The body of the pancreas was occupied by large, greyish white, firm tumor which had a glistening, mucoid surface. The tumor had compressed the main pancreatic duct, and the tail of the pancreas beyond the tumor was atrophic. Tumor metastases were found in the peripancreatic lymph nodes and one nodule was present in the liver. The brain weighed 1,300 gm. and a thin subarachnoidal hemorrhage extended over the convexity of the right cerebral hemisphere. The hemorrhage appeared to arise from a hematoma 2 cm. in diameter on the frontal pole of the right hemisphere, beneath which the cortical substance was destroyed. Examination of the cerebral venous sinuses revealed a thrombus occluding the superior sagittal sinus.

DR. ROBERT M. O'NEAL: The first thing I would like to point out is that microscopically no arterial thromboses were found; all thrombi were in veins. Figure 1 is a photomicrograph of the femoral vein with a large thrombus that fills its lumen, and is organizing at its point of attachment to the wall of the vein. There was no appreciable inflammatory reaction of the walls of any veins and the few lymphocytes present can be attributed to the presence of the thrombus alone. All the thrombi were of similar character and most were attached at only occasional points, obviously favoring embolization to pulmonary arteries such as did occur in this patient. The pulmonary arterial thrombi that were in branches to the upper left lobe were of varying ages, but all the thrombi we found in the pulmonary artery were organizing to some extent, indicating that no embolization occurred in the last day of life and therefore did not precipitate his terminal episode of collapse. The large hemorrhagic area in the upper left lobe was not necrotic but simply the result of massive intra-alveolar hemorrhage, almost certainly the origin of the patient's hemoptysis. There was massive bleeding into the lung, but not actual infarction as the alveolar walls were preserved. (Fig. 2.) These pulmonary emboli produced just enough damage to cause massive intra-alveolar hemorrhage; I believe we might call this an "incomplete" infarct. The thromboemboli probably originated from the veins of the leg.

The thrombus in the superior sagittal sinus that Dr. Tjien found on gross examination con-



FIG. 3. The wall of the sagittal sinus lies above and an older, organizing thrombus below. The wedge-shaped thrombus extending from the left is very recent and probably accounted for the cerebral infarct. Hematoxylin and eosin × 45.

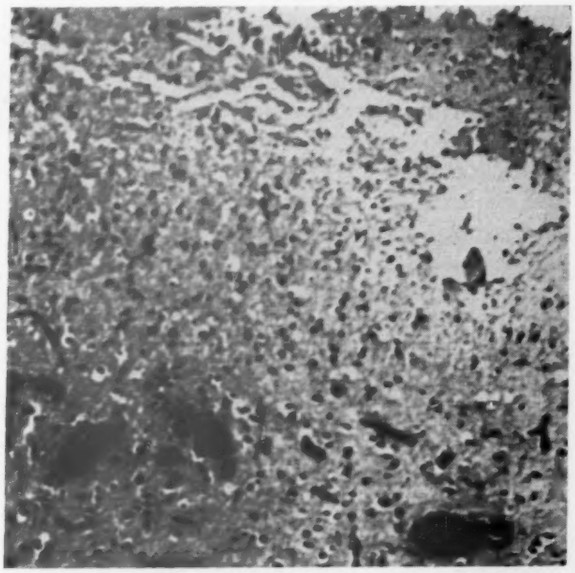


FIG. 4. A microsection of partially necrotic cerebral cortex, the site of the infarct, over which was a large blood clot. Hematoxylin and eosin × 110.

sisted of parts that appeared of different ages. In one portion there was organization at its point of attachment, so that it was somewhat older. However, there was a very recent thrombus overlying the older and this appeared to be the most recent of any thrombotic material found at any site. (Fig. 3.) We believe that the recent extension of the thrombus in the sagittal sinus is consistent with the history of the patient's severe collapse in coma and with our findings in the brain. The hemorrhagic infarct of the right frontal lobe of the brain was also extremely recent, with marked hemorrhage into a localized area of complete destruction of cortex, and

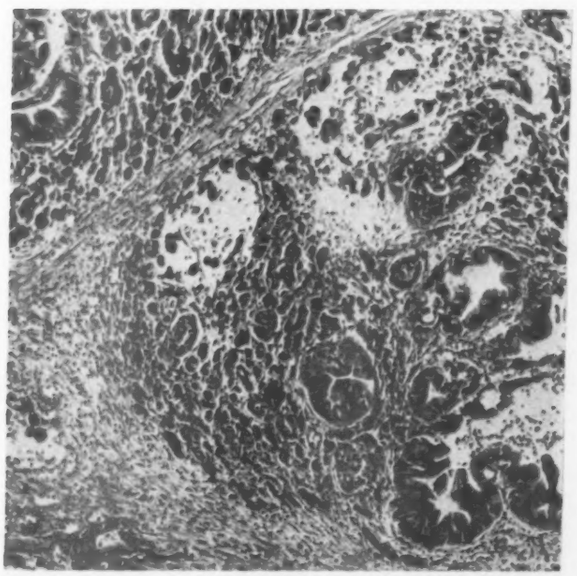


FIG. 5. A microsection of the junction between body and head of the pancreas. The large glandular carcinoma shown principally at the lower right, is invading the pancreatic tissue. Hematoxylin and eosin × 45.

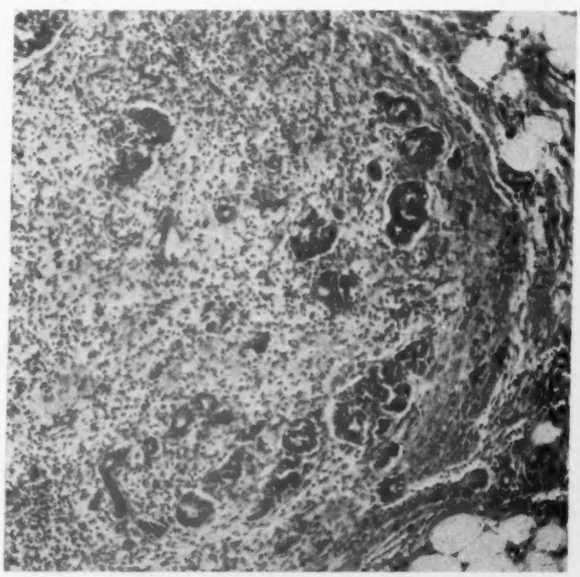


FIG. 6. The tail of the pancreas. Acini have been completely replaced by fibrous tissue but the darkly staining islets remain. Hematoxylin and eosin × 45.

around this marked focal hemorrhage especially into perivascular spaces. (Fig. 4.)

The carcinoma of the body of the pancreas was uniformly glandular and in many areas contained large amounts of mucus, and metastases in the liver and peripancreatic lymph nodes had an identical structure. Small thrombi were present in veins within and near the sites of tumor, but this is not necessarily of special significance because venous thrombi are found very commonly in an area of invasion by any tumor. There was a great deal of remaining normal pancreatic tissue in the head of the pancreas (Fig. 5) but the tail of the pancreas was completely fibrotic and atrophic; only islets of Langerhans remained, characteristic of the atrophy that follows complete obstruction of the pancreatic duct. (Fig. 6.)

Dr. Ira Gore* wrote a paper about five years ago in which he pointed out that this anatomic characteristic, a portion of the pancreas remaining intact, is characteristic of those cases of carcinoma of the pancreas that are associated with thrombosis. He postulated that since trypsin has a thromboplastin-like effect, the trypsin released into the blood stream from damaged pancreatic acinar cells, where tumor is invading pancreatic tissue, leads to thrombosis. References to other studies of this association between pancreatic carcinoma and venous thrombosis can be found in a recent article by Bell.*

Let me summarize the findings regarding thrombosis and events leading directly to death. There was pulmonary embolization but no evidence of a recent massive thromboembolization that would have led to his final collapse. A large cerebral infarct was present in the right frontal lobe, which we think was on the basis of an extension of a thrombus in the superior sagittal sinus and was responsible for the terminal episode of collapse which led to the patients death.

Primary anatomic diagnoses: Mucinous adenocarcinoma of the body of the pancreas with metastases to the peripancreatic lymph nodes and to the liver; atrophy of the acinar tissue of the tail of the pancreas secondary to obstruction of the pancreatic duct by tumor; phlebothrombosis in the legs with edema of both lower extremities; multiple organizing thromboemboli in large branches of the pulmonary artery to the upper left lobe with massive intra-alveolar hemorrhage and a 100 ml. hydrohemothorax on the left; and superior saggital sinus thrombosis, organizing, with hemorrhagic infarct of the right frontal lobe and subarachnoid hemorrhage over the right cerebral hemisphere, recent (consistent with history of collapse, ten hours).

* Gore, I. Thrombosis and pancreatic carcinoma. *Am. J. Path.*, 29: 1093, 1953.

* Bell, E. T. Carcinoma of the pancreas. *Am. J. Path.*, 33: 499, 1957.

Case Report

Hypogammaglobulinemia and Bronchial Asthma*

Report of Two Cases in Adults

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HYPOGAMMAGLOBULINEMIA, also known as globulin deficiency disease, is characterized (in the laboratory) by a marked decrease in serum gamma globulin and clinically usually by an increase in susceptibility to infection. Several comprehensive reviews [*1–3*] of both the clinical and theoretical aspects of this subject have been published recently. The fact that approximately eighty-five cases of hypogammaglobulinemia have been reported in the English literature since the original description by Bruton [*4*] in 1952 would indicate that it is by no means a rare finding.

The two principal types of hypogammaglobulinemia are congenital and acquired [*5*]. Congenital hypogammaglobulinemia is believed to be inherited as a sex-linked recessive factor. It is manifested in early childhood almost exclusively in males. Acquired hypogammaglobulinemia lacks an obvious family history in the majority of cases. It occurs in later life, equally in males and females.

Diseases of the lung constitute the most common types of infection found in conjunction with hypogammaglobulinemia. Recurrent pneumonia, bronchiectasis, empyema and pleurisy have been reported many times in patients with low levels of gamma globulin [*6,7*]. Extensive review of the literature has failed to elicit a report of coexisting bronchial asthma and hypogammaglobulinemia.

Inasmuch as there is considerable evidence to show that (certain or some) antibodies have chemical and physical properties similar to gamma globulin [*8*], many of the reported cases of hypogammaglobulinemia have been extensively investigated from an immunologic point of view [*9–12*]. These studies, which have been almost entirely concerned with antimicroorganismal antibodies of various types (agglutinins, antitoxins, neutralizing antibodies complement-fixing antibodies and hemagglutination-inhibiting antibodies) have demonstrated low to undetectable levels of circulating antibodies and a general unresponsiveness to antigenic stimulation.

No consideration has been given in these investigations to the possible relationship between skin-sensitizing (reaginic) antibodies and gamma globulin, although Fischer [*13*] and Zbar et al. [*14*] each reported on a patient with allergic symptoms and hypogammaglobulinemia. Fischer described his case as one of congenital absence of gamma globulin in a five year old boy, stating briefly that the patient had evidence of respiratory allergy and gave strongly positive cutaneous reactions on skin testing with unspecified allergens. Allergy to milk, penicillin and feathers was recorded in the case of acquired hypogammaglobulinemia by Zbar. Unfortunately, neither of these authors describe the exact clinical manifestations of their patient's sensitivities.

CASE REPORTS

CASE I. Lkh, a fifty-six year old housewife, has suffered from perennial bronchial asthma for twenty-two years. She was able to lead a normal life until December 1953, when her asthma became severe and incapacitating. From that time until the present she has never been completely free of cough, wheezing or dyspnea. These symptoms have necessitated numerous hospital admissions.

* From The Roosevelt Hospital, The Institute of Allergy, New York, New York.

Her asthma is considered to be primarily bacterial in origin. There is no obvious extrapulmonary source of infection. On skin testing she gives moderate (2 plus) reactions to dust and feathers.

Since September 1954 she has been receiving bronchodilators, hyposensitization and steroids continuously and ACTH intermittently. Any attempt to withdraw the hormones has resulted in prompt recurrence of symptoms. At present she is being maintained on a regimen of 15 to 20 mg. of prednisone per day.

For the past two years she has suffered recurrent bouts of fever rising to 102° to 103°F. for thirty-six to forty-eight hours. The patient also has complained of pretibial pain and difficulty in walking since January 1956; and the characteristic signs of a peripheral neuritis affecting the lower extremities has slowly developed. Extensive investigation, including a muscle biopsy and several L.E. preparations, has failed to elicit the cause of either the repeated bouts of fever or the neuritis.

Routine laboratory studies made on the last two hospital admissions (November 1956 and April 1957) were essentially normal even during the bouts of hyperpyrexia. Urinalysis occasionally has shown a few white cells and culture revealed a heavy growth of Proteus vulgaris and beta hemolytic streptococci. Cystoscopy revealed urethrotrigonitis with bullous edema of the bladder neck. This responded to Furadantin® and was not judged to be responsible for her elevated temperature. Roentgenograms of the chest, paranasal sinuses, gallbladder, complete gastrointestinal tract, and spine were within normal limits. The fasting blood sugar was elevated on two occasions (155 and 193 mg. per cent) but subsequent determinations and a glucose tolerance curve were within the range of normal. Chemical determinations of blood urea nitrogen, bilirubin, alkaline phosphatase, inorganic phosphorus and calcium yielded no abnormal findings. An electrocardiogram was within normal limits. Urinary 17-ketosteroid excretion and urinary calcium excretion were normal. Smears for malarial parasites and serological tests for febrile agglutinins were negative. Sputum culture yielded moderate growths of Neisseria catarrhalis, alpha hemolytic streptococci, and Diplococcus pneumonia. Blood cultures were negative.

In November 1956, bronchoscopy revealed chronic inflammatory changes in the trachea and major bronchi. Cytological studies of bronchial aspiration and sputum samples were negative for malignant cells.

In January 1956 an electrophoretic analysis of the patient's serum was performed, using the Tiselius method.* Her circulating gamma globulin level was found to be 240 mg. per cent. The results of subsequent analyses made at periodic intervals during the following eighteen months are shown in Table I. On November 27, 1956, she began to receive 20 ml. of gamma globulin* intramuscularly at monthly intervals, and from May 17 to June 19, 1957, she received the same dose at weekly intervals. (Table I.) Although clinically she has seemed to derive moderate benefit from treatment with gamma globulin, she still requires continuous prednisone therapy. Since instituting therapy with gamma globulin the patient has had no episodes of hyperpyrexia.

* All electrophoretic analyses recorded in this paper were performed in an Aminco-Stern apparatus with standard analytical cells [*15*] using Longsworth's barbiturate buffer [*16*].

CASE II. TMR, a fifty-four year old female school teacher, was admitted to the hospital in December 1955 for investigation of intractable bronchial asthma. The patient stated that as a child she was considered to be "sickly" and was particularly prone to recurrent respiratory infections. Because of her chronic illness her parents were forced to leave New York City. In rural surroundings the patient remained in good health until the age of twenty-three, when she again began to suffer from frequent respiratory infections, complicated this time with bronchial asthma. Since then she has had almost continuous asthma, as well as chronic pansinusitis and seven bouts of bronchopneumonia necessitating many admissions to various hospitals.

During the three years prior to admission to this hospital she had intermittently received relatively large doses of various steroid preparations and ACTH, and had derived only moderate benefit from them.

On admission the blood cell count was 10,300 per cu. mm. with a differential count of 77 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 20 per cent lymphocytes and 2 per cent monocytes. Urinalysis was within normal limits. Roentgenogram of the chest was essentially normal; those of the paranasal sinuses showed slight clouding of both maxillary antra and marked clouding of the right ethmoid sinus. An electrocardiogram was interpreted as normal. Sputum culture yielded a heavy growth of alpha hemolytic streptococci and a moderate growth of N. catarrhalis. A nasal culture taken from the right ethmoid region grew out a few colonies of Staphylococcus pyogenes. Skin testing revealed a slight (1 plus) reaction to dust, and moderate (2 plus) reactions to ragweed (1,000 protein nitrogen units per ml.). Other tests to common inhalants and foods were negative.

An electrophoretic analysis of her serum proteins by the Tiselius method showed a gamma globulin level of 460 mg. per cent.

Her bronchial asthma was thought to have a primary bacterial etiology, the paranasal sinuses

* Supplied by the American Red Cross as Poliomyelitis Immune Globulin (Human) said to contain a solution of the globulin fraction of pooled normal human plasma, 165 ± 15 mg. per ml. or 15 to 18 per cent total protein. Electrophoretic analysis of this lot disclosed it to be essentially 100 per cent gamma globulin.

TABLE I

ELECTROPHORETIC DETERMINATIONS

Date	Method	Total Protein by Biuret (gm./100 ml.) 7.23*	Albumin		Alpha Globulin		Alpha Globulin		Beta Globulin		Gamma Globulin	
			% 56.0*	gm./100 ml. 4.3*	% 7.2*	gm./100 ml. 0.5*	% 8.8*	gm./100 ml. 0.6*	% 13.1*	gm./100 ml. 0.9*	% 14.7*	gm./100 ml. 1.0*
						Case I						
1-13-56	E†	5.2	55.6	2.9	6.5	0.3	13.2	0.7	20.1	1.1	4.6	0.2
10-1-56	E	5.9	48.4	2.9	8.5	0.3	16.2	1.0	21.3	1.3	5.1	0.3
11-12-56	E	5.4	51.6	2.8	8.2	0.4	14.7	0.8	20.6	1.1	5.0	0.3
11-27-56	GG‡	...	....	...	...	...	....	...	....	....	...	....
12-26-56	GG	...	....	...	...	...	....	...	....	...	...	...
1-23-57	E	6.6	55.9	3.7	6.5	0.4	12.6	0.8	19.8	1.3	5.1	0.3
1-24-57	GG	...	....	...	...	...	....	...	....	...	...	...
2-25-57	GG	...	....	...	...	...	....	...	....	...	...	...
3-13-57	GG	...	....	...	...	...	....	...	....	...	...	...
4-30-57	E, GG§	5.8	52.9	3.1	7.7	0.5	12.7	0.7	20.2	1.2	6.5	0.4
5-1-57	E	5.5	54.5	3.0	7.7	0.4	12.5	0.7	19.4	1.1	6.0	0.3
5-6-57	E	6.0	54.9	3.3	7.6	0.5	11.3	0.7	19.8	1.2	6.3	0.4
5-17-57	GG	...	....	...	...	...	....	...	....	...	...	...
5-29-57	GG	...	....	...	...	...	....	...	....	...	...	...
6-5-57	GG	...	....	...	...	...	....	...	....	...	...	...
6-12-57	GG	...	....	...	...	...	....	...	....	...	...	...
6-19-57	E, GG§	6.3	57.3	3.6	5.6	0.4	12.3	0.8	18.8	1.2	6.1	0.4
6-26-57	GG	...	....	...	...	...	....	...	....	...	...	....
7-17-57	GG	...	....	...	...	...	....	...	....	...	....	...
7-31-57	GG	...	....	...	...	...	....	...	....	...	...	...
8-14-57	GG	...	....	...	...	...	....	...	....	...	...	...
9-4-57	GG	...	....	...	...	...	....	...	....	...	...	...
10-9-57	GG	...	....	...	...	...	....	...	....	...	...	...
10-16-57	E, GG§	7.1	56.4	4.0	5.6	0.4	11.6	0.8	17.5	1.2	8.9	0.6
						Case II						
12-21-56	E	6.6	54.5	3.6	7.6	0.5	15.7	1.0	15.2	1.0	7.0	0.5
1-15-57	GG	...	....	...	...	...	....	...	....	...	...	...
2-15-57	GG	...	....	...	...	...	....	...	....	...	...	...
3-15-57	GG	...	....	...	...	...	....	...	....	...	...	...
4-15-57	GG	...	....	...	...	...	....	...	....	...	...	...
4-24-57	E	6.7	57.3	3.8	6.9	0.5	9.9	0.7	18.0	1.2	8.0	0.5
8-5-57	E	6.8	56.0	3.8	5.5	0.4	10.6	0.7	19.7	1.3	8.2	0.6
8-9-57	E	7.1	56.0	4.0	6.3	0.4	11.1	0.8	18.6	1.3	8.0	0.6

* Normal values: see reference [*15*] (Reiner, Fenichel and Stern).
† E = bleeding for electrophoresis.
‡ GG = administration of 20 cc. of gamma globulin.
§ Gamma globulin given in afternoon; blood for electrophoresis drawn in morning.

acting as a focus of infection. While in the hospital she was treated with ACTH, prednisone, chloramphenicol, streptomycin, potassium iodide and bronchodilators. At the time of discharge she had improved considerably.

Following discharge she received 20 ml. of gamma globulin intramuscularly at monthly intervals in conjunction with her usual medications. After four months of therapy her physician was of the opinion that no significant improvement in her condition could be attributed to the gamma globulin. Her serum gamma globulin level after four months of treatment was 530 mg. per cent.

COMMENTS

The results of electrophoretic analyses of the serums, and of total protein determinations, along with the absolute concentration of the individual serum components, are given in Table I. Observations on the variations from normal are based on the data of Reiner, Fenichel and Stern [*15*], and on our own estimate of error.

In Case I, Lkh, data on nine bleedings are presented. (Table I.) The first three bleedings were made prior to the administration of gamma globulin. After starting therapy with gamma globulin, six bleedings were made at regular intervals during the next nine months. Gamma globulin therapy is being continued.

The serum albumin, expressed in per cent of total proteins, was essentially normal, except for the second bleeding which was below normal. The absolute concentration of albumin was

always low, except for the last bleeding which was normal. The $alpha_1$ globulin was essentially normal in all bleedings. The $alpha_2$ globulin was slightly high percentagewise, except for the second bleeding which was considerably elevated. By absolute concentration, the $alpha_2$ globulin was essentially normal, except the second bleeding which was high. The beta globulin was above normal percentagewise, and in absolute concentration remained in the high normal range.

The gamma globulin was always low, the first bleeding being the lowest There is indication that the gamma globulin level rose with treatment, and that this higher level was being maintained. The increase in gamma globulin in the last bleeding is significant. The total protein was always below normal, or in the low normal range, the first bleeding being the lowest. The values have not risen consistently, but appear to fluctuate. The increase in the last bleeding is significant.

In Case II, Tmr, data on four bleedings are presented. (Table I.) In the four months between the first and second bleedings, gamma globulin was administered at monthly intervals. Gamma globulin therapy was then completely stopped.

The albumin and the $alpha_1$ globulin were essentially normal in all bleedings. The $alpha_2$ globulin was found to be above normal on the first bleeding and was essentially normal for all three subsequent bleedings. The beta globulin was normal on the first bleeding, increased to the high normal or above normal range in the last three bleedings.

The gamma globulin in all four bleedings was always lower than normal, the lowest value being the first bleeding. The gamma globulin level then rose slightly, and this new level was being maintained. The increase may not be significant. The total protein was always normal or low normal. On successive bleedings, it appeared to exhibit consistent although slight increases.

In the two cases herein reported the serum proteins appear to have been altered toward more or less normal values. These changes resulted in (1) increased total protein, (2) decreased $alpha_2$ globulin and (3) increased gamma globulin which may or may not be significant.

The etiology of the gamma globulin deficiency in the two cases reported in this paper is difficult to determi[illegible], as after extensive investigation no underlying disease processes were discovered. The ages of these patients seem to place them in the acquired type of hypogammaglobulinemia.

It is interesting to speculate about the possible relationship between hypogammaglobulinemia and bronchial asthma. If there is any relationship between these two disease entities, it is probable that the bronchial asthma is secondary to the hypogammaglobulinemia, rather than a cause of it. The work of Jencks et al. [*17*] lends support to this assumption. They analyzed the serum proteins, by filter paper electrophoresis, in thirteen cases of bronchial asthma and found the circulating gamma globulin to be at normal levels in eleven cases, and above normal in two cases. Cooke et al. [*16*] report on fourteen cases of chronic intrinsic asthma. Four patients had "above normal" gamma globulin values and "in several others" the gamma globulin was "slightly elevated." None were reported as being low. It may be tentatively concluded from these reports that hypogammaglobulinemia is not an expected sequel of bronchial asthma. It would seem, then, that in the two cases cited either the converse is true or that there is no cause-and-effect relationship between the two conditions.

These two cases are also of interest in regard to current discussions in the literature about the chemical nature of the skin-sensitizing (reaginic) antibody. Depending on the fractionation technic employed, various workers have identified skin-sensitizing antibodies with the $alpha_2$, $beta_1$, $beta_2$ or gamma globulin components of human serum [*18–20*]. There is no general agreement as to whether skin-sensitizing activity is limited to one of these serum components or distributed among several.

If skin-sensitizing antibodies were identified with gamma globulin, like most other human antibodies, a minimal or absent allergic response would be expected in cases of hypogammaglobulinemia. The two cases which have been described had severe bronchial asthma in the presence of low levels of circulating gamma globulin. There are three possible explanations for this combination of circumstances: (1) skin-sensitizing antibodies are entirely associated with gamma globulin, and the residual gamma globulin contains sufficient antibody to produce severe allergic symptoms, (2) skin-sensitizing antibodies are associated with serum fractions other than gamma globulin, and (3) skin-sensitizing antibodies were not responsible for

the production of allergic symptoms in these patients.

The third possibility requires further elaboration. Both patients were considered on clinical grounds to have primarily bacterial allergy. The exact nature of the immune mechanisms in bacterial allergy is not well understood, but it is a generally accepted fact that they are not mediated by circulating antibodies. There is considerable evidence to show that the development of bacterial allergy is dependent on a cellular rather than a humoral mechanism [*21–23*]. Thus, even if circulating skin-sensitivity antibody were entirely associated with gamma globulin, it would be possible for a patient with hypogammaglobulinemia to suffer from severe bacterial asthma. In fact, a bacterial asthma might be more likely to develop in such a person than in a comparable patient with normal levels of gamma globulin because of the increased susceptibility to infection.

Another factor of possible etiological significance is the large amount of 17-hydroxysteroid compounds received by both patients over a period of several years. It is conceivable that these hormones may have some influence on gamma globulin synthesis or destruction. This question has been explored by Good and Kelley [*24*], who found no evidence of abnormal pituitary adrenal corticoid function in patients with hypogammaglobulinemia.

The results of treatment with gamma globulin were encouraging in Case 1, as the patient had no bouts of hyperpyrexia and less asthma.

It is possible that the dose of gamma globulin (0.1 mg. per kg. of body weight) was too low to afford adequate protection to our patients. Several workers have reported that 0.1 gm. of gamma globulin per kg. of body weight, given at monthly intervals, was sufficient to induce a beneficial response in patients with extremely low levels of gamma globulin [*25,26*]. On the other hand, Martin et al. [*11*] found that they had to administer a "loading" dose of 0.3 gm. per kg. of body weight, followed by maintenance doses of 0.1 gm. per kg. of body weight every two weeks in order to obtain satisfactory results in a patient with a serum gamma globulin level of 230 mg. per cent. It is probable that some patients require larger doses than others to achieve clinical improvement, and that the dosage required is not directly proportional to the degree of gamma globulin deficiency.

The levels of circulating gamma globulin in these two patients were somewhat above those generally reported with the diagnosis of hypogammaglobulinemia. As this condition becomes more widely recognized, a larger number of cases of this type will probably be discovered.

SUMMARY

Two cases of coexisting hypogammaglobulinemia and bronchial asthma occurring in women between the ages of fifty and sixty are described. This association of diseases has not been reported previously. Treatment with intramuscular gamma globulin resulted in improvement in one of the patients. The relationship between circulating skin-sensitivity antibodies and gamma globulin is discussed.

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The American Journal of Medicine

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Volume XXV
JULY TO DECEMBER
1958

THE AMERICAN JOURNAL OF MEDICINE, INC.
NEW YORK MCMLVIII

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Printed in the United States of America

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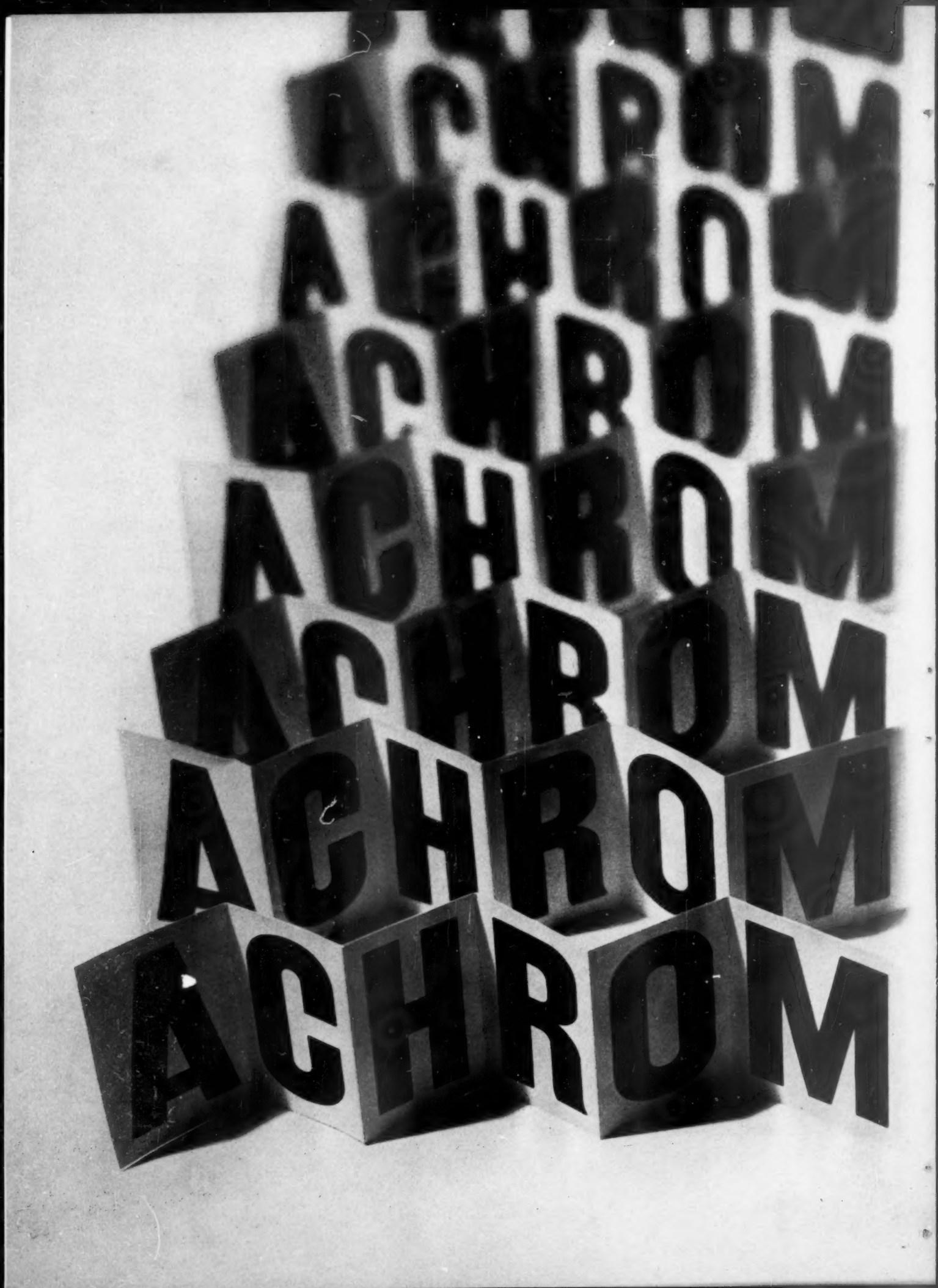
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Other studies show the important role of the B vitamins in antibody formation. Thus, *Nutrition Reviews*[2] reports: "Present evidence indicates that certain B vitamins, notably pyridoxine, pantothenic acid and folacin, play a significant role in antibody synthesis." According to Pollack and Halpern,[3] "Under-nutrition leads to increased susceptibility to infection and decreased resistance to established disease." And "vitamin deficiency states also may adversely influence circulating antibodies."

Halpern[4] reports that "good nutrition is important for optimal resistance to infection, for a superior tissue capability to cope with disease and injury, and for maximum antibody production . . . nutrition participates in the prophylaxis against most acute infections . . ."

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—the remarkably efficient skeletal muscle relaxant, unique in chemical formulation, and outstanding for sustained action and relative freedom from adverse side effects.

PUBLISHED REFERENCES: 1. Carpenter, E. B.: Southern Medical Journal 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Little, J. M., and Truitt, E. B., Jr.: J. Pharm. & Exper. Therap. 119:161, 1957. 4. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: J. Am. Pharm. Assn., Sci. Ed. 46:374, 1957. 5. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 6. Park, H. W.: J.A.M.A. 167:168, 1958. 7. Truitt, E. B., Jr., and Patterson, R. B., Proc. Soc. Exper. Bio. & Med. 93:422, 1957. 8. Truitt, E. B., Jr., Patterson, R. B., Morgan, A. M., and Little, J. M.: J. Pharm. & Exper. Therap. 119:189, 1957.

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Robaxin Beneficial in 95.6% of Cases of Acute Skeletal Muscle Spasm[1, 2, 5, 6]

CONDITION	NO. PATIENTS	RESPONSE			
STUDY 1[1]		"marked"	moderate	slight	none
Skeletal muscle spasm secondary to acute trauma	33	26	6	1	—
STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamenteous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
STUDY 4[6]		"significant"			
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
TOTALS	138	104 (75.3%)	28 (20.3%)	4	2

THE JOURNAL of the American Medical Association

"In the author's clinical experience, methocarbamol has afforded greater relief of muscle spasm and pain for a longer period of time without undesirable side effects or toxic reactions than any other commonly used relaxants . . ."[2]

THE JOURNAL of the American Medical Association

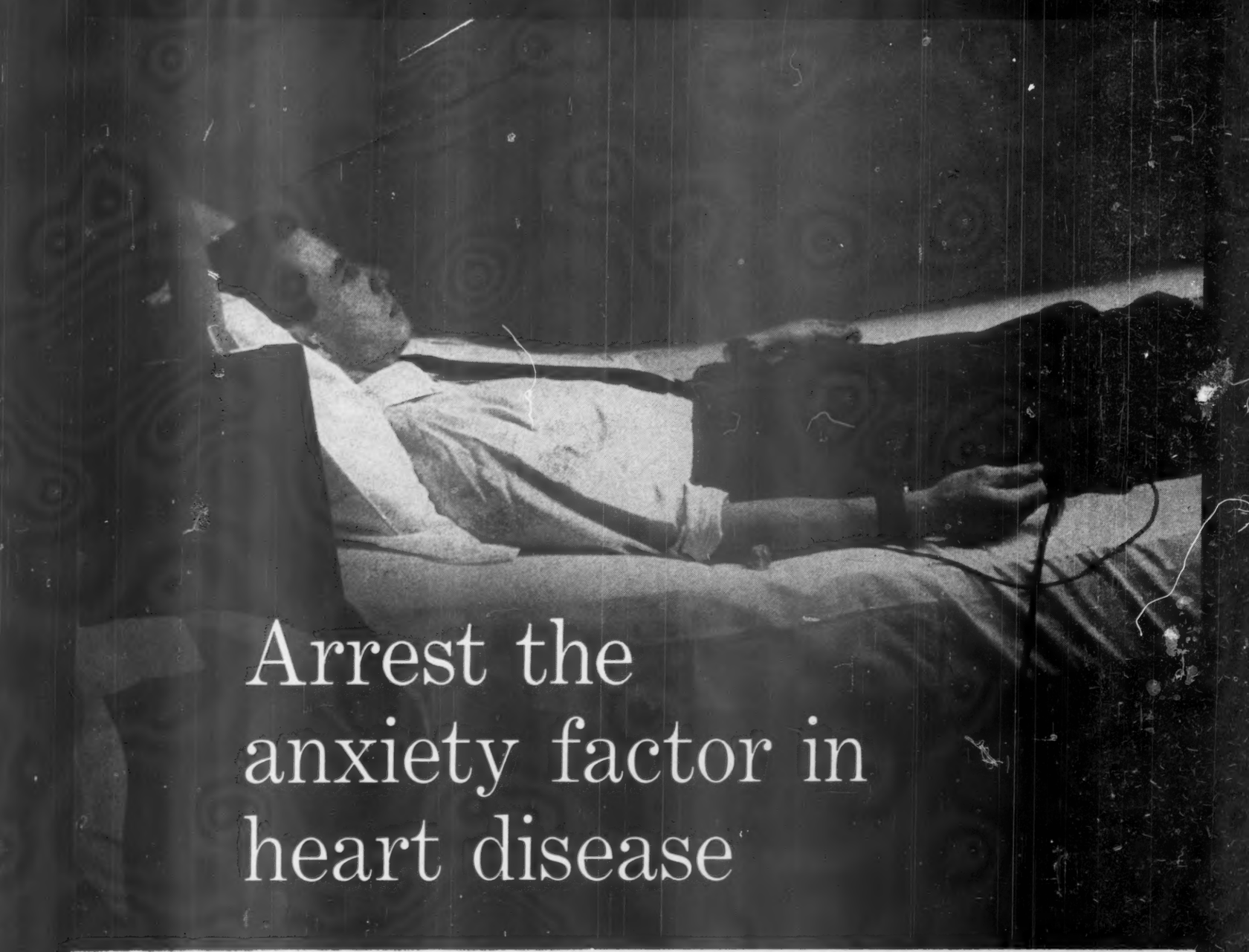
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"Now Mommy is fine... and she said I could help cook... but Daddy said just the tea"

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U. S. Pat. 2,628,185

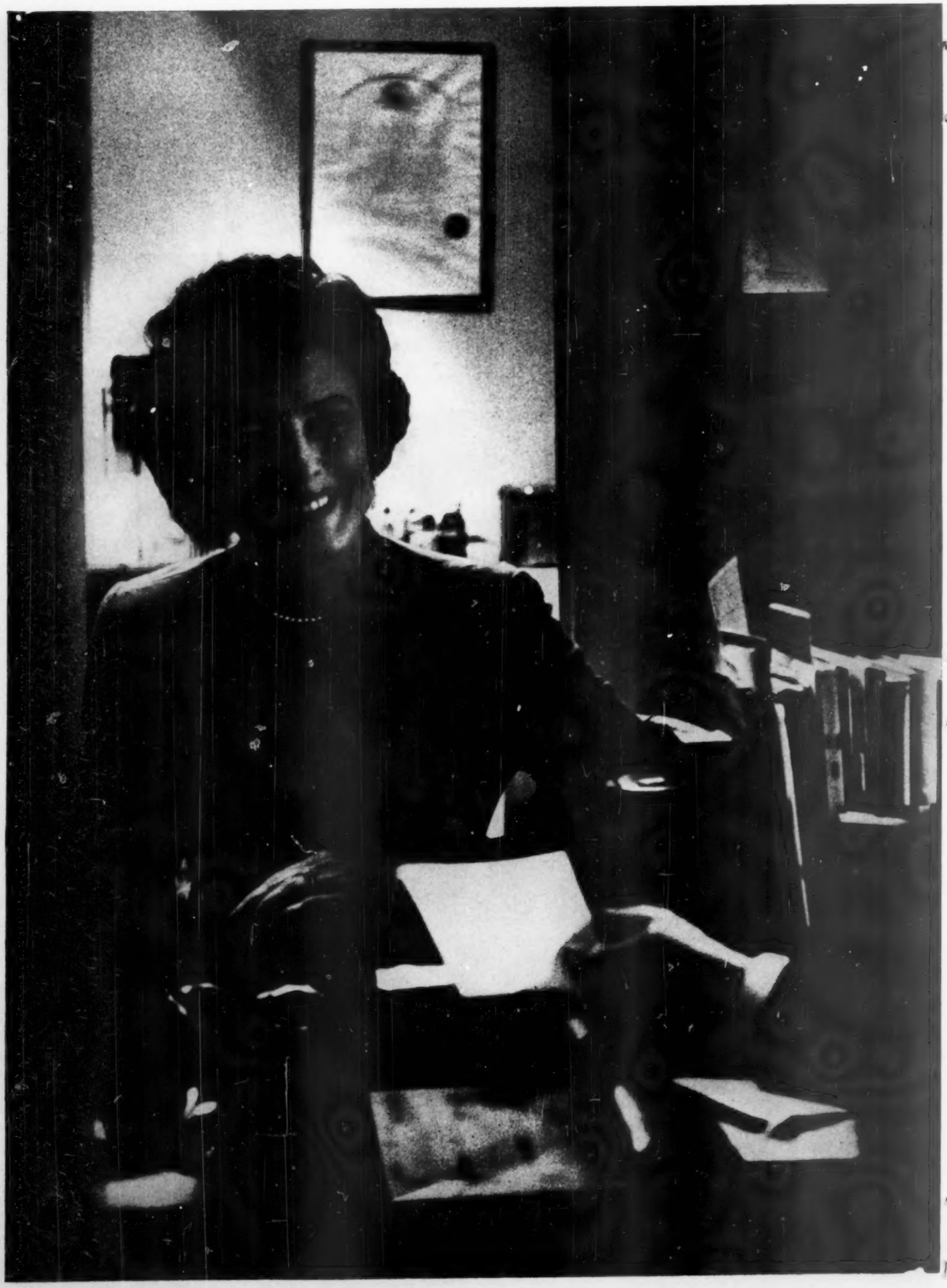
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REFERENCES: 1. Carlozzi, M.: Antibiotic Med. & Clin. Therapy 5:146 (Feb.) 1958. 2. Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 5:52 (Jan.) 1958. 3. Marlow, A. A., and Bartlett, G. R.: Glucosamine and leukemia, Proc. Soc. Exp. Biol. & Med. 84:41, 1953. 4. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 5. Nathan, L. A.: Arch. Pediat. 75:251 (June) 1958. 6. Cornbleet, T.; Chesrow, E., and Barsky, S.: Antibiotic Med. & Clin. Therapy 5:328 (May) 1958. 7. Stone, M. L.; Sedlis, A., Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy 5:322 (May) 1958. 8. Harris, H.: Clin. Rev. 1:15 (July) 1958.

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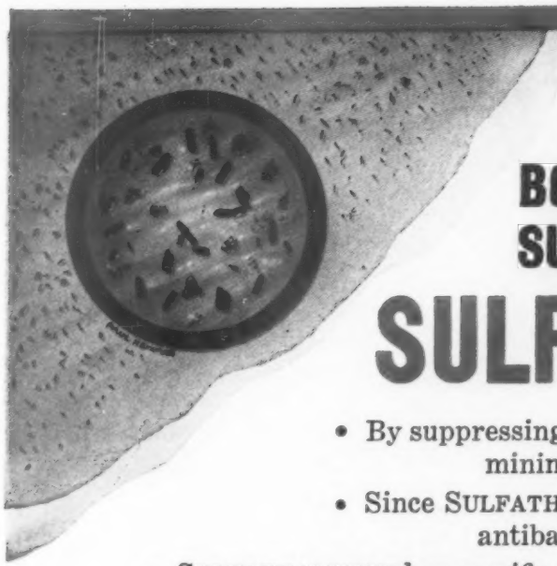
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1. *Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Card.* 1:395, *March 1958.*
2. *Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology* 8:504, *Dec. 1957.*

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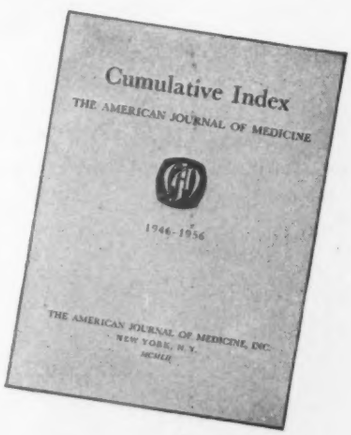
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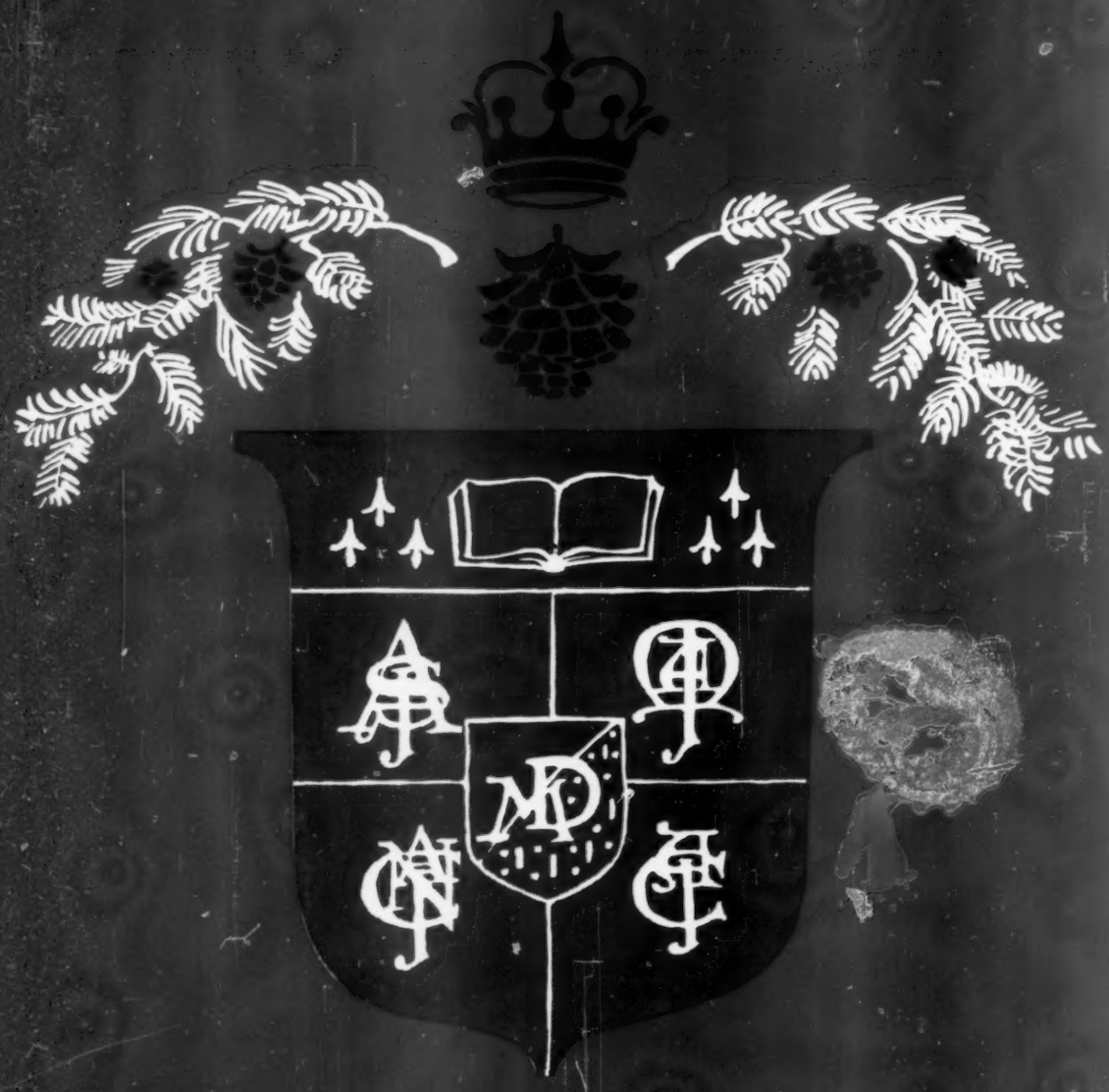
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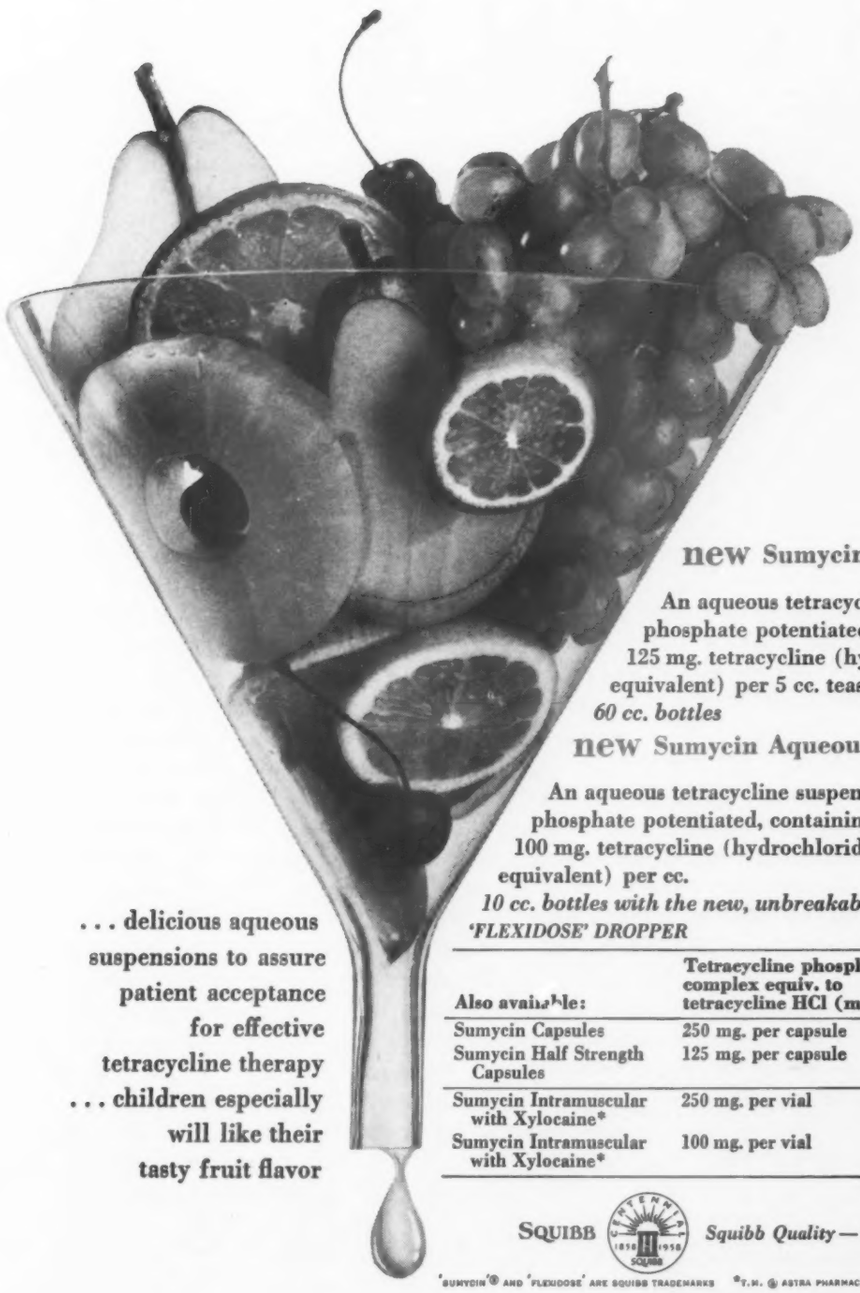
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1. Muir, A., and Cossar, I. A.: Brit. M. J. *II*:7-12 (July 2) 1955.

*TRADEMARK, REG. U.S. PAT. OFF. — TOLBUTAMIDE, UPJOHN

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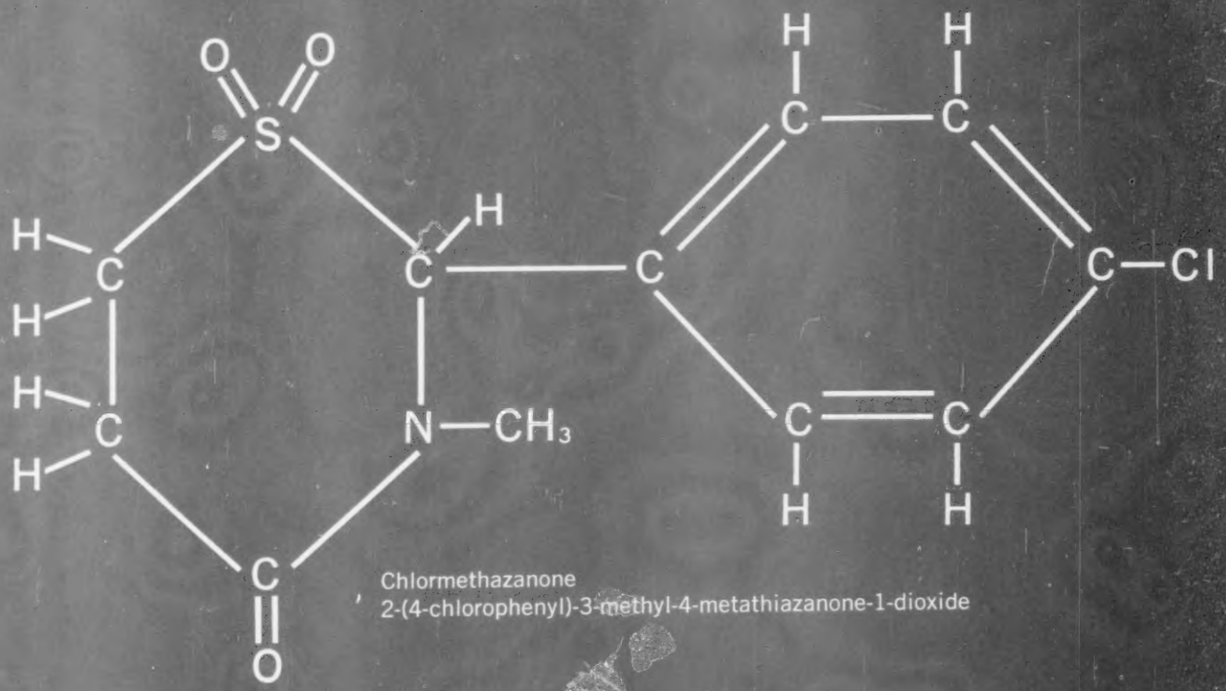
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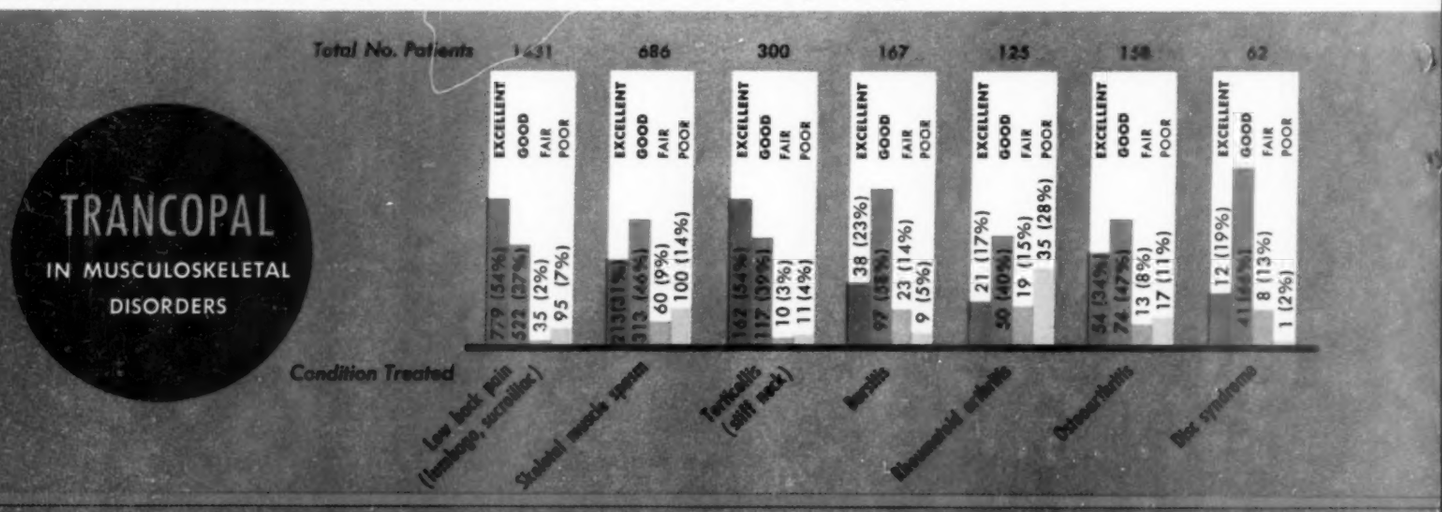
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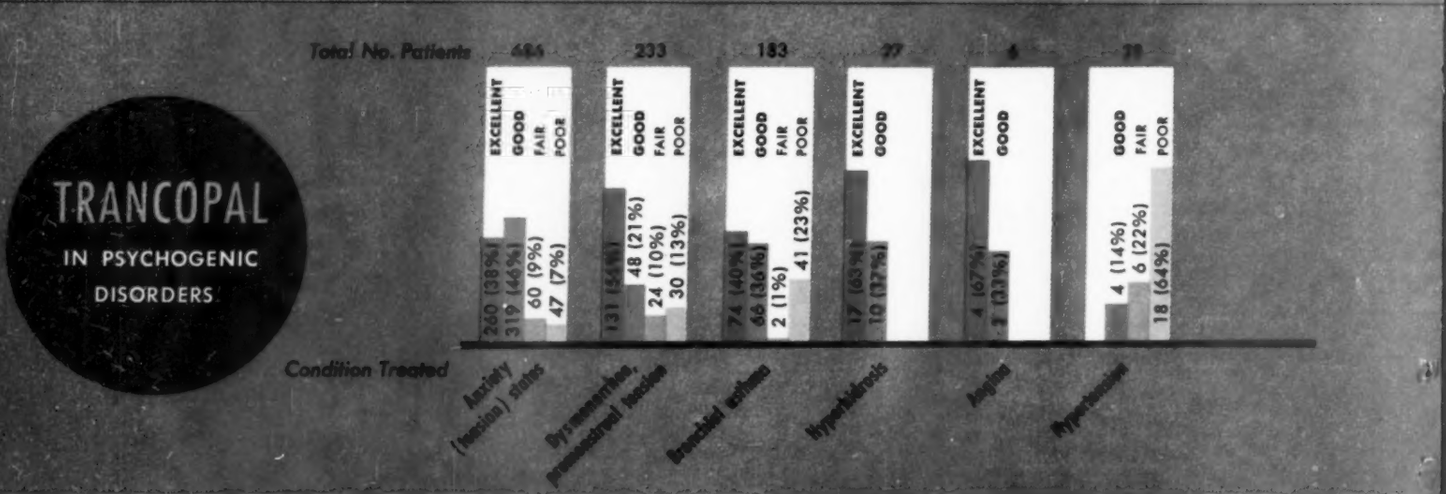
offering new freedom for your patients... from muscle spasm, from tension and anxiety, from side effects

* **tran-qui-lax-ant** (tran'kwi-lak'sant) [< L. tranquillus, quiet; L. laxare, to loosen, as the muscles]

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In musculoskeletal disorders, 91 per cent effective.

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Lower incidence of side effects than with zoxazolamine, methocarbamol or meprobamate.

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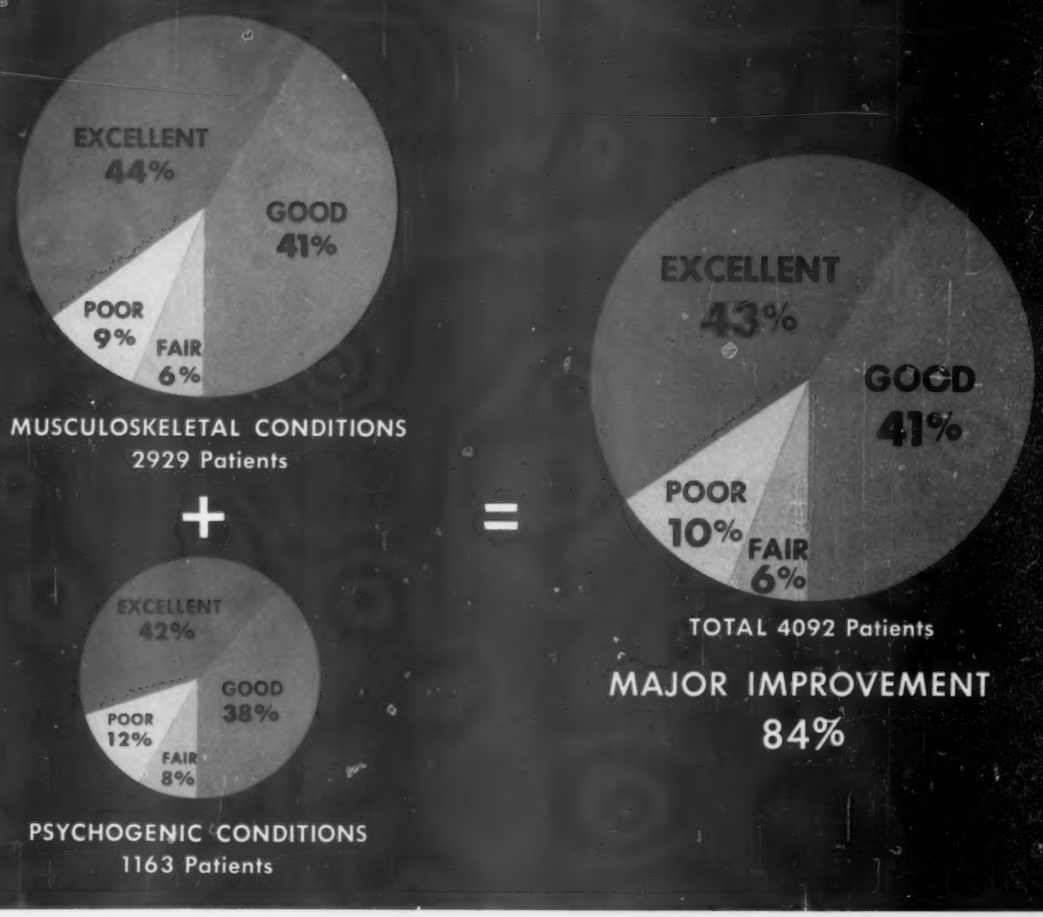
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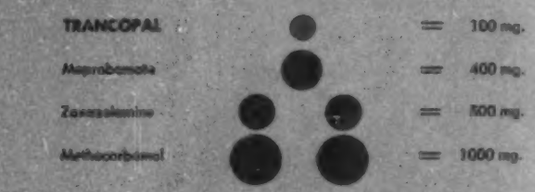
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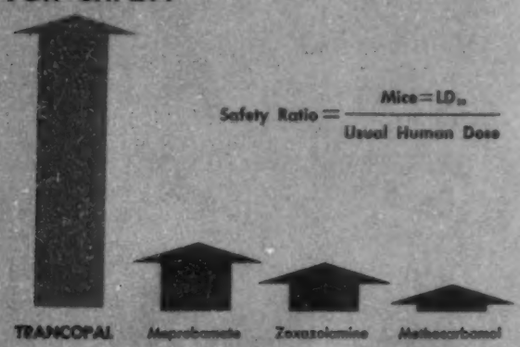


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Considering the usual human dose, Trancopal, the first true "tranquilaxant," is four to ten times as potent per milligram.

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$$\text{Safety Ratio} = \frac{\text{Mice} = LD_{50}}{\text{Usual Human Dose}}$$



Comparative pharmacologic tests showed that Trancopal is up to thirteen times as safe, or up to thirteen times less toxic. The measure of safety was the LD_{50} in mice/usual human dose.

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A clinical comparison in low back pain, torticollis, bursitis and anxiety states showed that Trancopal is up to four times as effective. Each of 40 patients received all four drugs in random rotation for several days. While each of the four drugs gave some relief, only the one providing the most effective relief was recorded.

INDICATIONS

Musculoskeletal
- Low back pain (lumbago)
- Neck pain (torticollis)
- Bursitis
- Rheumatoid arthritis
- Osteoarthritis
- Disc syndrome
- Fibrositis
- Joint disorders (ankle sprain, tennis elbow, etc.)
- Myositis
- Postoperative myalgias

Psychogenic
- Anxiety and tension states
- Dysmenorrhea
- Premenstrual tension
- Asthma
- Emphysema
- Angina

Neurologic
- Muscle spasm in paralysis agitans, multiple sclerosis, hemiplegia, poliomyelitis

TRANCOPAL thoroughly evaluated clinically

"In the treatment of conditions associated with skeletal muscle spasm there was a high percentage of satisfactory results (excellent, good or fair) in 310 patients (94%) out of 331 treated. . . . In 120 patients with simple anxiety or tension states results were satisfactory in 114 (95%). Dosage of chlormethazanone in all cases was 100 mg. t.i.d. As well as relieving the anxiety or tension state, chlormethazanone also allowed these patients to resume their usual occupations." (Lichtman)

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Dosage: One Caplet (100 mg.) orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours.

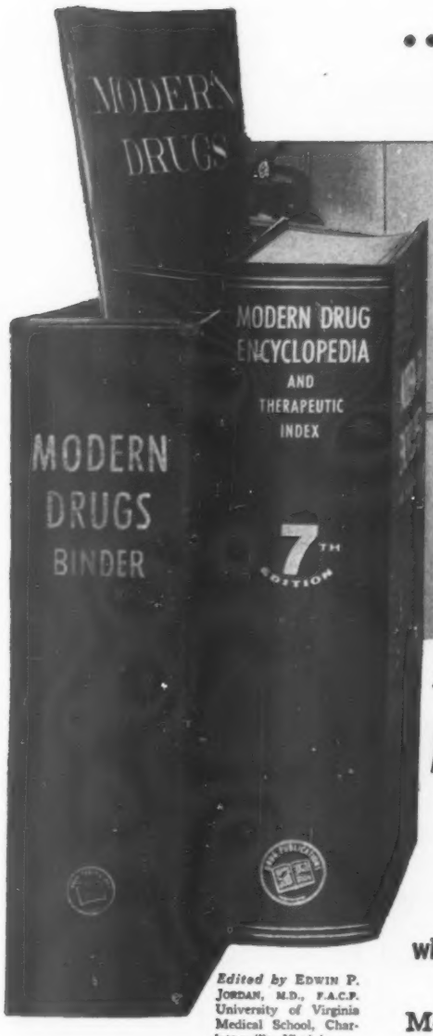
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• Baker, A. B.: Modern Med. 26:140, April 15, 1958. • Cohen, A. I.: In preparation. • Cooperative Study, Department of Medical Research, Winthrop Laboratories. • Gesler, R. M., and Coulston, F.: Toxicol. & Appl. Pharmacol. To be published. • Gesler, R. M., and Surrey, A. R.: J. Pharmacol. & Exper. Therap. 122:24A, Jan., 1958. • Gesler, R. M., and Surrey, A. R.: J. Pharmacol. & Exper. Therap. 122:517, April, 1958. • Lichtman, A. L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958. • Surrey, A. R.; Webb, W. G., and Gesler, R. M.: J. Am. Chem. Soc. 80:3469, July 5, 1958.

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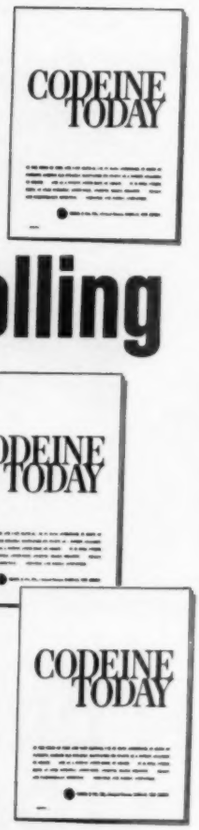
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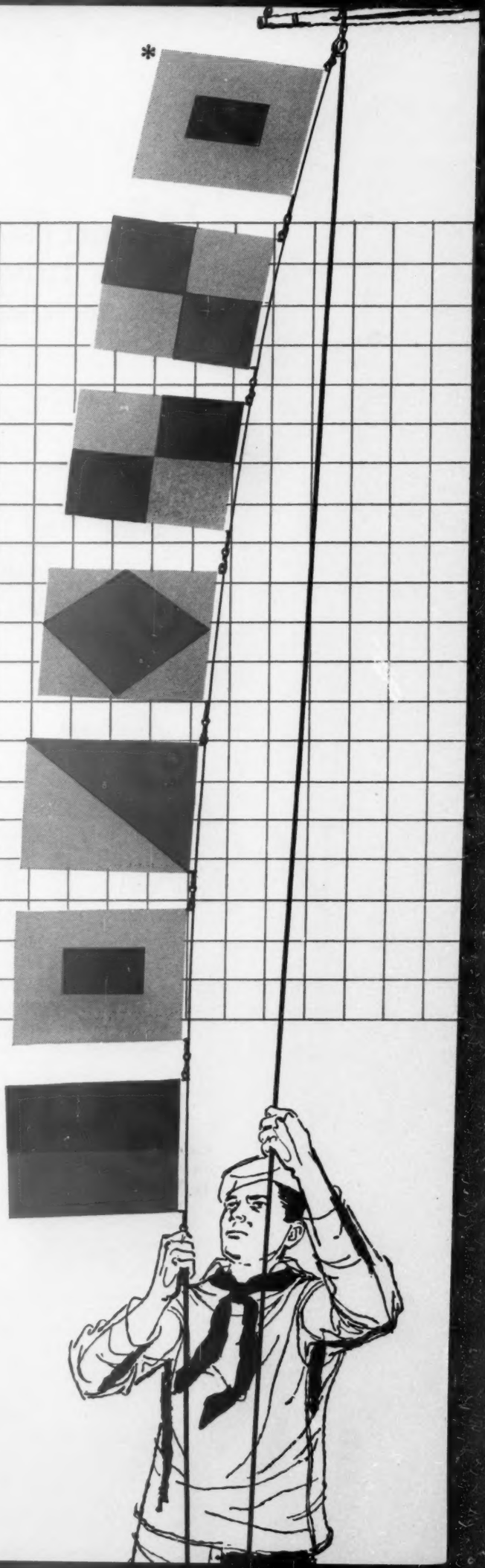
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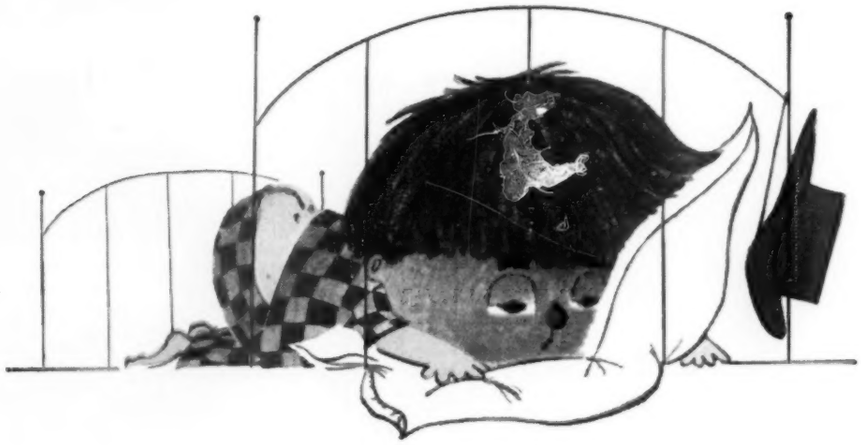
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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

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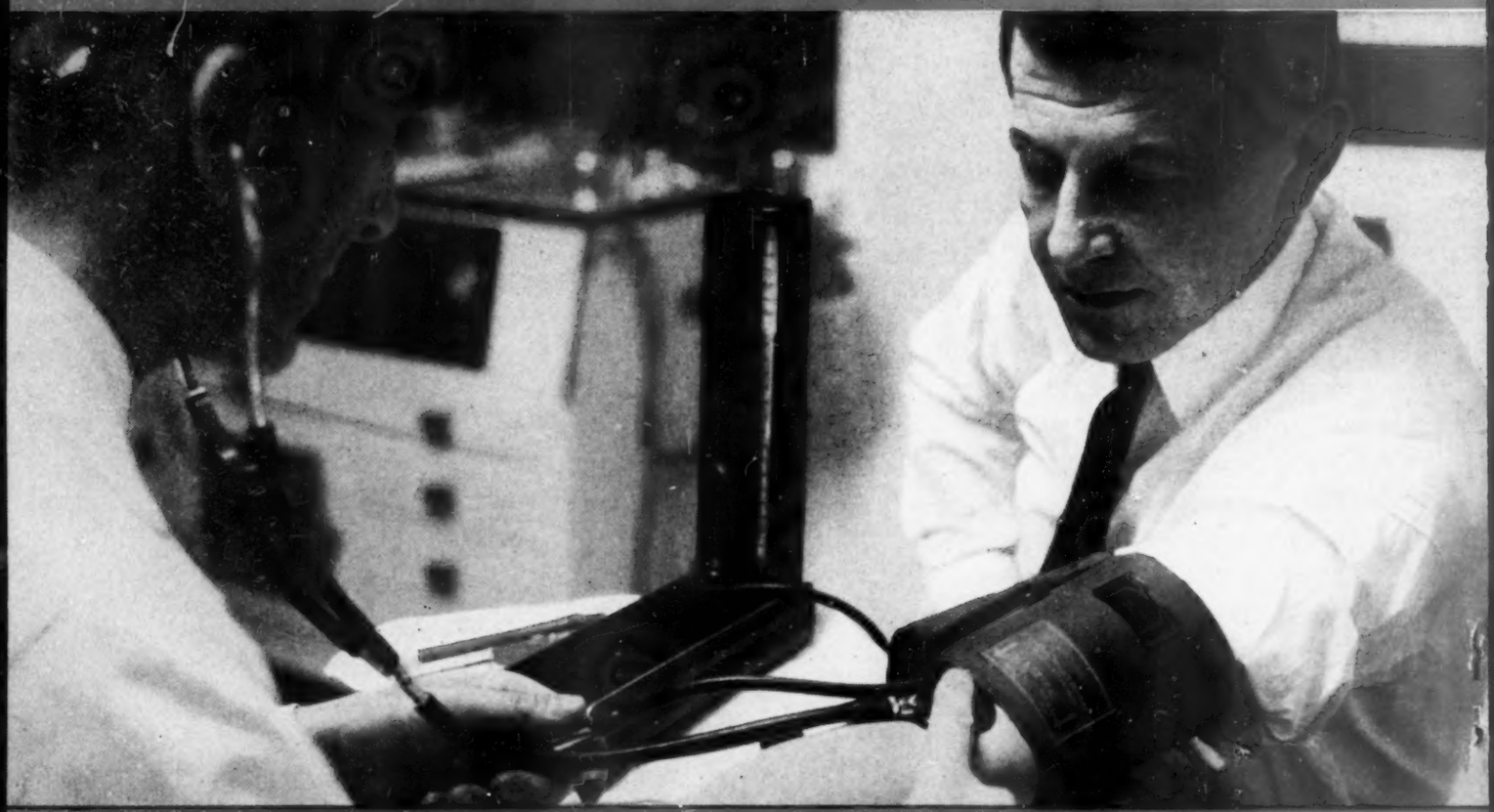
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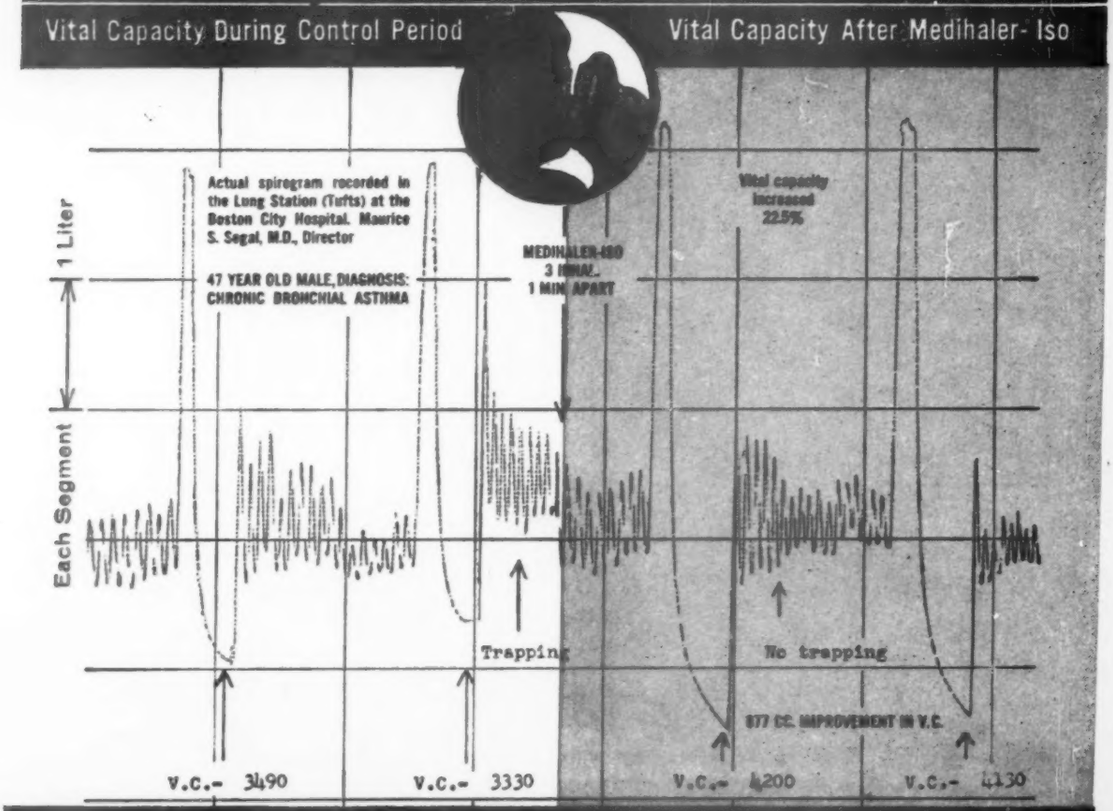


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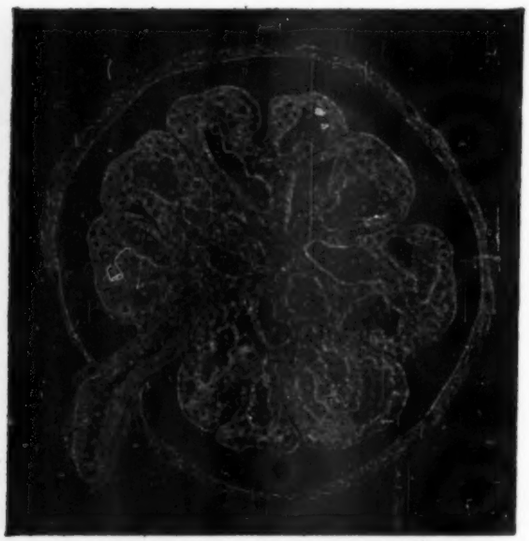
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